## Clinical staging of Non-Small Cell Lung Cancer

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# CLINICAL STAGING OF NON-SMALL CELL LUNG CANCER

**David Jonathan Heineman**

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# CLINICAL STAGING OF NON-SMALL CELL LUNG CANCER

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# GENERAL INTRODUCTION AND OUTLINE

## LUNG CANCER IN THE NETHERLANDS

Lung cancer causes most cancer-related deaths in the world, despite intense anti-tobacco policy and evolving therapies.[1-4] Tobacco use accounts for 80-90% of lung cancer cases.[5] Non-small lung cancer (NSCLC) is the most common subtype (80-90%). In the Netherlands, there were 13,262 new cases of lung cancer in 2018 (incidence rate of 78/100,000 inhabitants), of which 9,650 patients had NSCLC. There were 7,226 new male patients and 6,036 new female patients with lung cancer in 2018. The average five-year survival for a patient with any type of lung cancer was 19% in the Netherlands in the period 2010 to 2015[6], and comparable five-year survival rates have been reported in the United States in the same period.[7] The five-year survival of the non-small cell subtype (NSCLC) was 23%, compared to 6% for small cell lung cancer (SCLC).[7]

Accurate diagnosis and staging, which is the focus of this thesis, is important to direct optimal treatment planning. Treatment options are dependent on the extent of disease spread. Current ESMO guidelines on early and locally advanced NSCLC[8] advise the following treatment strategies depending on the stage of the disease:

- in early stage NSCLC or in a tumor with hilar lymph node metastasis, surgery is the treatment of choice, combined with adjuvant chemotherapy in patients having hilar or unforeseen mediastinal lymph node metastasis after pathological review, and for tumor > 4cm
- for patients with stage I NSCLC who are medically inoperable or have comorbidities, and for patients who refuse surgery, stereotactic ablative radiotherapy (SABR) is the preferred treatment
- for patients presenting with resectable mediastinal lymph node metastasis, surgical multimodality treatment can be considered
- in patients with extensive mediastinal lymph node infiltration, non-surgical multimodality treatment is advised.

In the Netherlands, patterns of care have changed after the introduction of SABR in 2004, especially in the elderly population presenting with early stage NSCLC. The percentage of elderly patients (>75 years) with stage I NSCLC receiving surgery remained stable in the period 2001-2009, at 37%. However, use of radiotherapy in the same population increased from 31% to 38%. Elderly patients not undergoing curative-intent treatment decreased in the mentioned period from 32% to 25%.[9] In a more recent study patterns of care

from 2010-2015 were investigated: for stage I disease, patients aged 65-74 years received surgery in 55%, compared to 29% SABR and 6% conventional radiotherapy. Patients aged >75 years received surgery in 27% in this period, compared to 42% SABR and 11% conventional radiotherapy. In stage II disease surgery was used in 65% in patients aged 65-74 years, SABR in 5% and conventional radiotherapy in 10%. For patients aged >75 years these percentages were 35%, 11% and 24%, respectively.[10] In a recently presented study these trends were confirmed: use of surgery remains constant in elderly patients in stage I disease, use of radiotherapy has increased and fewer patients receive no curative intent treatment over the years.[11]



In locally advanced, stage IIIA disease, a minority of patients received an operation in the Netherlands: between 2010 and 2013 15% of patients was operated, with a minority receiving induction therapy. Chemoradiotherapy with curative intent was used in 45% of patients.[12] This therapy was also treatment of choice in patients with stage IIIB disease during 2010-2014 in the Netherlands, with 48% of patients receiving chemoradiotherapy and only 2.2% receiving a treatment that included surgery.[13]

**Staging guidelines**

Patients with NSCLC are staged according the TNM Classification of Malignant Tumours from the Union for International Cancer Control.[14] Table 1 and 2 show the TNM-descriptors and the different stages according the 7th edition, which has been used for this thesis.[15] Figure 1 depicts the nodal chart for lymph node stations and zones according to the International Association for the Study of Lung Cancer (IASLC). Accurate staging is complicated, the lymph nodes (N descriptor) in particular, as shown previously by several reports.[16-23] Even after the broad introduction of the integrated fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT), nodal staging accuracy in clinical practice varies, depending on which modalities are used to stage nodes after the PET-CT (see Table 3).

According to current guidelines, several findings on computed tomography (CT) or PET-CT implicate further investigation of mediastinal lymph nodes:[8,24-26]

- mediastinal lymph node with a short axis diameter >1 cm on CT-scan, or uptake on PET-CT (N2 node)
- hilar lymph node with a short axis diameter >1 cm on CT-scan, or uptake on PET-CT (N1 node)



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- central tumor
- tumor ≥3 cm
- primary tumor without uptake on PET-CT

As a first step in mediastinal nodal investigations, minimally invasive techniques such as endoscopic ultrasound (EUS) and endobronchial ultrasound (EBUS) are currently advised. Once cytology obtained from suspected lymph nodes by EUS/EBUS is negative, (video)mediastinoscopy should follow.[27]
In clinical stage III disease a magnetic resonance imaging (MRI) scan of the brain is also advised. Distant metastases can be identified on the MRI of the brain or the PET-CT (see Figure 2).[25,26]

Thorough clinical staging precedes solid treatment planning, preferably by treating physicians during multidisciplinary discussion. Next to physical fitness and patient preferences, the clinical stage determines the initial treatment. For approximately 20% of patients with NSCLC, surgery is the treatment of choice.[28] Surgical resection typically consists of an anatomical resection of the lung parenchyma (pneumonectomy, (bi)lobectomy, segmentectomy) plus a hilar and mediastinal lymph node dissection - or sampling. Once resected, the specimen can be pathologically reviewed, and a definite pathological stage can be aggregated.
Discordance between clinical and pathological stage is defined as a non-matching clinical stage compared to the pathological stage in a certain patient. This has to be prevented, since it carries the risk of withholding the best treatment.
Both up-staging and down-staging is possible. For example, a patient can shift to a higher pathological stage if a tumor invades the parietal pleura, which was not expected on imaging before the operation. The same is true for unforeseen mediastinal involvement of lymph nodes (unforeseen N2). Down-staging in particular occurs by overestimating the size of the tumor (T-descriptor) on CT-scan, for example due to peritumorous inflammation, atelectasis, tumor infiltration or edema.[29]
With discrepancy of clinical and pathological stage, treatment might be inferior or the patient can be withhold from certain treatment. For example, a patient who has clinical stage IB, subsequently planned for surgical resection, but turns out to have pathological stage IIIA because of unforeseen N2-involvement, would have been treated differently in the

situation where N2 involvement was proven before treatment planning (either chemoradiotherapy or induction followed by surgery). Vice-versa, suspicious PET-positive lymph nodes, guiding treatment towards definitive chemoradiotherapy, could be surgically treated if tissue diagnosis proved that the PET-scan was false positive. So, omitting invasive mediastinal staging in such a patient could cause overtreatment and prevent surgical resection, to date the best chance of cure for these patients.
These examples illustrate the importance of proper mediastinal pre-treatment staging. The approach to mediastinal nodal staging is largely based on the ASTER trial, which showed a sensitivity of 79% for surgical staging with (video)mediastinoscopy alone, a sensitivity of 85% for endosonography alone and 94% of endosonography followed by (video) mediastinoscopy.[27] Recent guidelines therefore advise to start with EBUS and/or EUS, and when these prove negative (i.e. no tumor cell on cytology), this should be followed by a (video)mediastinoscopy.



## CLINICAL AUDITING

Clinical auditing was designed to assess quality of medical care and to benchmark treatment outcome. It can be used to analyze variation in patterns of care and outcomes. Benchmarking results can be used as a feedback tool for hospitals or individual caregivers to provide insight in ways to improve quality of care.[30-33] In 2012, the Dutch Lung Cancer Audit (DLCA), initially named the Dutch Lung Surgery Audit (DLSA), was introduced to evaluate and monitor the quality of lung operations in the Netherlands.[34,35]

In this thesis data from the Dutch national audit on lung cancer care (DLCA) was used to analyze several aspects of clinical staging of NSCLC. Our objective was to get insight in clinical staging in daily practice and to construct recommendations to improve clinical staging and guideline adherence.

The DLCA is described in **Chapter 2**, in which the historic perspective of the initiation of the DLCA is delineated. **Chapter 3** describes the problem of staging inaccuracy of NSCLC in the Netherlands by analyzing all patients with NSCLC in 2013 and 2014.

The clinical relevance of correct clinical staging is highest in those patients who would receive a different (potentially more successful) therapy, once they were staged correctly. In **Chapter 4** and **Chapter 5** patients with stage I NSCLC and patients with locally advanced lung cancer, in particular resectable stage IIIA-N2, are analyzed to investigate whether these patients were unfairly denied correct treatments. Patients with stage I disease can be treated with either surgery or SABR, but if a patient has a pathological stage II or higher, surgery and adjuvant chemotherapy are recommended. In patients with resectable stage IIIA-N2 NSCLC guidelines recommend induction chemo(radiotherapy) before a resection, if resected.

In **Chapter 6**, an analysis of all patients that were staged by (video) mediastinoscopy from 2012 to 2016 is shown. We describe the number and location of biopsied lymph nodes by (video)mediastinoscopy, and how this relates to the lobe that contains the tumor. With these data we were able to critically appraise the technical performance of (video)mediastinoscopy, and guideline adherence by surgeons performing this procedure.

In **Chapter 7** we present combined data from Denmark and the Netherlands. These are two Western European countries with a high standard of health care, but a different health care system and governance: in Denmark health care is government funded and directed, and lung cancer surgery is highly centralized in 4 hospitals. In the Netherlands health care companies pay for health care, and lung surgery is performed in 43 hospitals (in 2016). We were primarily interested in whether there would be a possible effect of health care system and centralization on lung cancer care, and also in the accuracy of clinical staging of NSCLC in these two countries.

**Chapter 8** is a review of the implications for adjuvant chemotherapy in relation to clinical staging of NSCLC. For patients who are treated by SABR and not surgery for early stage NSCLC, no lymph nodes are harvested. As a consequence, in these patients, the pTNM is unknown and possible unforeseen N1 or N2 nodal involvement not recognized, and thus, at least in some patients, adjuvant chemotherapy is denied. **Chapter 9** contains a response on two invited commentaries regarding this review (Chapter 8), putting our invited review and the commentaries into perspective.

**TABLE 1.** Definitions for T, N and M descriptors according to the 7th edition of the TNM.[14]

| **T (Primary Tumor)** | |
|---|---|
| **Tx** | Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy |
| **T0** | No evidence of primary tumor |
| **Tis** | Carcinoma in situ |
| **T1** | Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*a* |
| **T1a** | Tumor ≤ 2 cm in greatest dimension |
| **T1b** | Tumor > 2 cm but ≤ 3 cm in greatest dimension |
| **T2** | Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm). Involves main bronchus, ≥ 2 cm distal to the carina. Invades visceral pleura. Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung. |
| **T2a** | Tumor > 3 cm but ≤ 5 cm in greatest dimension. |
| **T2b** | Tumor > 5 cm but ≤ 7 cm in greatest dimension. |
| **T3** | Tumor > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina*a* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe. |
| **T4** | Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe. |

**TABLE 1.** Continued

| **N (Regional Lymph Nodes)** | |
|---|---|
| **Nx** | Regional lymph nodes cannot be assessed. |
| **N0** | No regional lymph node metastasis. |
| **N1** | Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension. |
| **N2** | Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s). |
| **N3** | Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s). |

| **M (Distant Metastasis)** | |
|---|---|
| **Mx** | Distant metastasis cannot be assessed. |
| **M0** | No distant metastasis. |
| **M1** | Distant metastasis. |
| **M1a** | Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion.*b* |
| **M1b** | Distant metastasis. |

*a* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1.

*b* Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

**TABLE 2.** Descriptors, T and M categories, and proposed stage groupings according to the 7th edition of the TNM.[14]

| Occult carcinoma | Tx | N0 | M0 |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage Ia | T1a, b | N0 | M0 |
| Stage Ib | T2a | N0 | M0 |
| Stage IIa | T2b<br>T1a, b<br>T2a | N0<br>N1<br>N1 | M0<br>M0<br>M0 |
| Stage IIb | T2b<br>T3 | N1<br>N0 | M0<br>M0 |
| Stage IIIa | T1a, b, T2a, b<br>T3<br>T4 | N2<br>N1, N2<br>N0, N1 | M0<br>M0<br>M0 |
| Stage IIIb | T4<br>Any T | N2<br>N3 | M0<br>M0 |
| Stage IV | Any T | Any N | M1 |

**TABLE 3.** Median sensitivity and specificity of invasive diagnostic modalities to stage the mediastinum according to the American College of Chest Physicians (ACCP) clinical practice guidelines.[26]

| Modality | Sensitivity | Specificity |
|---|---|---|
| Mediastinoscopy | 78% | 100% |
| Videomediastinoscopy | 89% | 100% |
| EBUS | 89% | 100% |
| EUS | 89% | 100% |
| Combination EUS/EBUS | 91% | 100% |

EBUS = endobronchial ultrasound
EUS = endoscopic ultrasound

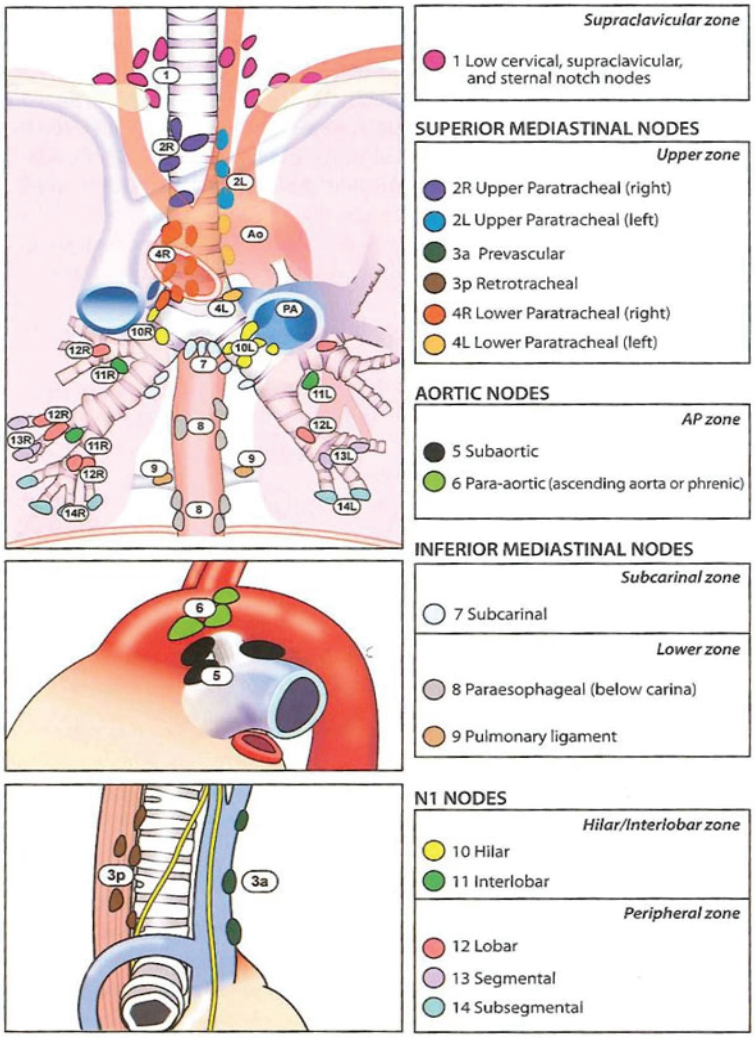


**FIGURE 1.** Nodal chart for lymph node stations and zones according to the International Association for the Study of Lung Cancer (IASLC).

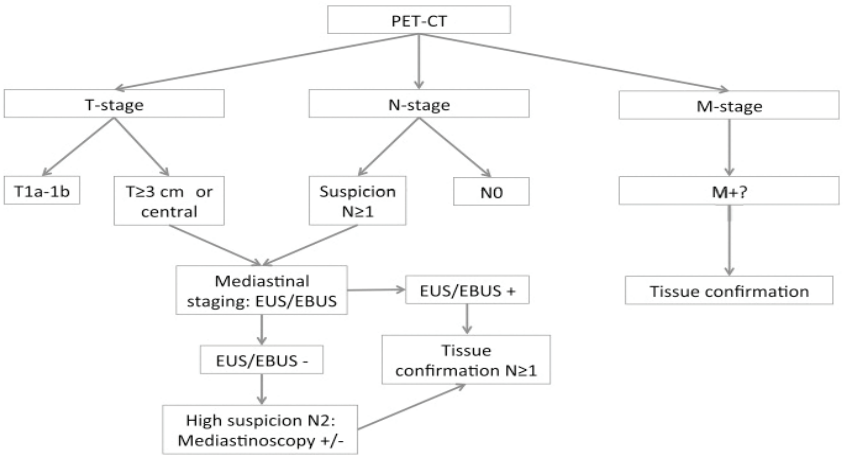


**FIGURE 2.** Staging algorithm according to the European Society of Thoracic Surgeons (ESTS)[24]

PET-CT = positron emission tomography - computed tomography
EBUS = endobronchial ultrasound
EUS = endoscopic ultrasound

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# DUTCH LUNG SURGERY AUDIT: A NATIONAL AUDIT COMPRISING LUNG AND THORACIC SURGERY PATIENTS

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*Ann Thorac Surg. 2018;106:390-7.*

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## ABSTRACT

### Background

The nationwide Dutch Lung Surgery Audit (DLSA) started in 2012 to monitor and evaluate the quality of lung operations in the Netherlands as an improvement tool. This outline describes the establishment, structure, and organization of the audit by the Dutch Society of Lung Surgeons (NVvL) and the Dutch Society of Cardiothoracic Surgeons (NVT), in collaboration with the Dutch Institute for Clinical Auditing. In addition, the first 4-year results are presented.

### Methods

The NVvL and NVT initiated a web-based registration, including weekly updated online feedback for participating hospitals. Data verification by external data managers is performed on regular basis. The audit is incorporated in national quality improvement programs, and participation in the DLSA is mandatory by health insurance organizations and the National Healthcare Inspectorate.

### Results

Between January 1, 2012, and December 31, 2015, all hospitals performing lung operations participated, and a total of 19,557 patients were registered from which almost half comprised lung cancer patients. Nationwide the guideline adherence increased over the years, and 96.5% of lung cancer patients were discussed in preoperative multidisciplinary teams. Overall postoperative complications and mortality after non-small cell lung cancer operations were 15.5% and 2.0%, respectively.

### Conclusions

The audit provides reliable benchmarked information for caregivers and hospital management with potential to start local, regional, or national improvement initiatives. Currently, the audit is further completed with data from nonsurgical lung cancer patients, including treatment data from pulmonary oncologists and radiation oncologists. This will ultimately provide a comprehensive overview of lung cancer treatment in the Netherlands.

## INTRODUCTION

Clinical auditing has been recognized as a valuable tool to assess and improve the quality of medical care. It is used to evaluate variation in health care processes and the resulting outcomes. Benchmarked information on hospital performance is returned to caregivers to enable them to improve patient outcome.[1-3] This information is presented in the form of quality of care indicators that are derived from the data collected in the audit and can be used to make (variation in) quality of health care more transparent.[4] Furthermore, clinical audits can produce data with additional value to prospective studies, because patients who are not eligible for trials are included and comprise a considerable part of the real-world patient population. In 2007 the European Society of Thoracic Surgeons introduced a European database to benchmark performance for lung operations carried out by individual institutes in different countries with the purpose to improve quality of care.[5] Similar national audits for lung cancer treatment evolved in the United Kingdom and Denmark.[6,7]

In 2000, the Dutch Association of Physicians in Chest Medicine and Tuberculosis (Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose), Dutch Society of Cardio-Thoracic Surgery (Nederlandse Vereniging voor Thoraxchirurgie; NVT) and Dutch Society of Lung Surgeons (Nederlandse Vereniging voor Longchirurgie; NVvL) introduced quality standards for lung operations in the Netherlands, as an inherent part of their professional quality system, including certification of non- cardiothoracic surgeons and consultation of surgical departments. A minimum annual volume standard of 20 anatomic parenchymal resections (pneumonectomy, (bi)lobectomy, segmentectomy) for each hospital was set. Moreover, in 2012 the NVvL initiated the initiated the Dutch Lung Surgery Audit (DLSA), facilitated by the Dutch Institute for Clinical Auditing (DICA).[8] The primary goal is to monitor the adherence to quality standards, variation in clinical practice, and outcomes of lung operations between hospitals.

In 2014, most cardiothoracic surgeons of the NVT started to register their patients in the DLSA, first on a voluntary base but from January 2015 it became mandatory, which made the DLSA a nationwide population- based clinical audit, covering all non-cardiac thoracic procedures, hospitals, and patients in the Netherlands.

Primary objective of this study is to describe the establishment, organizational structure, quality indicators, and 4-year results of the nationwide DLSA, with the hypothesis that initiating of the DLSA will lead to

early improvements in quality of care for non-small cell lung cancer (NSCLC) operations.

## MATERIAL AND METHODS

### Organizational structure

In the Netherlands lung operations are performed by two surgical departments: general surgeons trained and certified in noncardiac thoracic operation (GLSs) and cardio-thoracic surgeons (CTSs). In 2012, the NVvL made participation mandatory for their members. In 2013, the National Healthcare Inspectorate and health insurance companies obliged hospitals performing lung operations to participate in the DLSA. The NVvL and NVT formed a joint scientific committee with mandated GLSs and CTSs, an epidemiologist from the Netherlands Cancer Registry, and supportive staff from DICA. This scientific committee is responsible for development of the data set and for defining quality indicators for lung operations.

### Database

The database contains four patient groups: lung cancer operation, mediastinal operation, metastasectomy, or benign lung and thoracic procedures (Figure 1). For lung cancer resections, the database contains 340 variables that concern case-mix variables (patient and tumor characteristics), variables describing the diagnostic and (peri-)operative process, including time periods, type of operation, surgical outcomes (morbidity and mortality), and pathologic results (radicality of resection in combination with pathologic staging). Lung transplantations and thoracoscopic sympathectomy or thymectomy are yet not included.

### Online data entry and data quality

Data are entered in a secure web-based registration interface. High-quality data assurance is assured by clear definitions of data entry points, incorporation of conditions and validations for each data entry point in the interface, and online feedback of missing or unreliable data at the patient level. The last step is data verification by an external organization. Trained personnel randomly verify hospital data from the database with the electronic patient records. In case of discrepancy an external committee decides what data should be entered in a report sent to the hospital. These discrepancy reports can be accessed by the general public.

**Quality indicators**

Supported by DICA, the scientific committee and external parties (such as the health insurance companies and scientific medical societies) developed an indicator set, comprising structure, process, and outcome indicators. The main structure indicator is hospital volume, [9-11] the process indicators focus on preoperative staging [12-16] and timing of operation,[7-21] and outcome indicators focus on mortality and complications. Outcome indicators are risk-adjusted, calculated over 2 years, for potential confounders, such as age, comorbidities, lung function, and tumor stage (case-mix adjustment). The indicator set and the case-mix model are (re-)evaluated by the scientific committee on an annual basis to guarantee accordance with changes in evidence-based guidelines.



**Online benchmarked feedback**

Quality indicator results are presented to participating hospitals in a secured web-based environment entitled MyDLSA. Results of an individual hospital are benchmarked against other hospitals in funnel plots by using national average and 95% confidence intervals. Participating hospitals can distinguish their own results in these funnel plots from a highlighted dot, the results of other hospitals are shown with anonymous dots (Figure 2).

**Statistical analysis**

Results of quality indicators and outcomes are presented concerning patients with NSCLC who had an operation from January 1, 2012, until December 31, 2015. Low-volume hospitals are defined as performing <20 parenchymal lung resections, medium volume as performing 20 to 50 resections, and high volume as doing more than 50 resections. Hospital volume was calculated for every single year. Differences in quality indicator results over time are tested for significance with the Chi-square trend test.

## RESULTS

In 4 years 19,557 patients were included and were undergoing lung, thoracic, or mediastinal operations. The largest group (38%, n = 7,422) was for a benign operation, followed by lung cancer operation (37.9%, n = 7,395), mediastinal operation (17.3%, n = 3,381), and metastasectomies (6.9%, n = 1,359). In the first year (2012) of registration, 41 hospitals entered patients in the DLSA. This number increased to 43 hospitals in 2015, despite participation of 15

cardiothoracic hospitals. This increase can be explained by centralization of lung operations. At the start 15 hospitals (36.6%) did not meet the minimum volume requirement compared with only one (2.5%) hospital in 2015 (Figure 3). Several low-volume hospitals stopped performing lung operations or star- ted to collaborate with other hospitals to meet the minimum criteria. A definite increase in high volume hospitals was observed, from 8 hospitals in 2012 to 19 hospitals in 2015.

**Database**

No important differences in patient and tumor characteristics of NSCLC patients registered in the period 2012 to 2014 and 2015 were observed (Table 1). An increase in the use of video-assisted thoracic surgery (VATS) for the resection of NSCLC was observed during the study period (Figure 4). Over 4 years a small increase in the use of VATS was observed with a maximum of 64.8% in 2014, accompanied by an increase in conversion to thoracotomy rate from 8.8% to 10.9%.

**Process indicators**

The percentage of patients being discussed in postoperative multidisciplinary team meetings increased from 81.5% to 96.5% ($p<0.001$) (Table 2). Besides, the percentage of patients with a clinical TNM stage being registered increased from 74.3% to 93.0% ($p<0.001$). Nevertheless, the percentage of patients who had a discrepancy between clinical and pathologic TNM stages initially decreased from 59.3% to 50.5% but increased to 54.5% in 2015.

**Outcome indicators**

During the study period the 30-day or in hospital mortality after parenchymal lung resection for NSCLC was low and varied between centers from 0 and 5.3% for lobectomies or segment resections and 0 and 22.8% for pneumonectomies (overall 30-day mortality: 1.5% to 2.9%). No substantial change was observed. A decline in severe complications (30-day mortality, re-intervention, intensive care unit admittance greater than > 3 days or length of stay > 14 days) was seen from 13.7% to 11.7%, followed by an increase to 15.5% in 2015. Frequency of irradical (R1/R2) resections decreased from 6.4% to 5.5% in 2012 to 2014 and increased to 6.3% in the last year, although these changes did not reach statistical significance.

## COMMENT

Within the first 4 years, the DLSA has shown strong commitment of (non-) cardiothoracic surgeons in the Netherlands to participate in this nationwide registry. During the study period adherence to the national NSCLC Guidelines improved considerably, which highlights the main purpose of the DLSA: quality assurance for every thoracic surgical patient in the Netherlands.[22] By setting new minimal requirements and monitoring these on a hospital level in the DLSA, major quality improvements can be achieved in a relatively small time period. By identifying positive outliers based on benchmarked indicator results, the DLSA can provide professionals with actionable information to improve their care and patients with valid information to choose the hospital of their preference. In addition, the NVvL founded a special expert committee, which offers its expertise and experience to hospitals with unfavorable outcomes, by offering extra training and by reviewing their care pathway.



At the end of 2015, all hospitals with noncardiac lung surgeons, and cardiothoracic surgical centers participated in the DLSA. The audit shows that almost all hospitals meet the minimal volume requirement of 20 parenchymal resections a year. Because of minimum volume requirements and centralization, hospitals with more than 50 parenchymal resections a year increased to a total of 19 (46.3%) in 2015.

Damhuis and colleagues[23] described that approximately 22% of the hospitals performed more than 50 parenchymal resections in the period 2005 to 2010. Apart from the increase of high-volume hospitals, the total number of hospitals decreased from 79 in 2005 to 69 hospitals in 2010 and further to 43 in 2015. So the last decade shows a considerable movement of centralization of lung operations in the Netherlands.

After introduction of VATS techniques in the late 1990s in the Netherlands, more than one-half of the parenchymal resection are now started and completely executed with VATS technique. This number is relatively high compared with other European countries (mean 21.7%).[24] The increased conversion rate could be explained by treating more difficult patients with extensive disease. In the near future, the introduction of novel techniques such as robotic-assisted thoracic surgery or uniportal VATS can be monitored.

The percentage of patients with recorded cTNM was low in 2012 (74.3%), but after setting a minimal standard of 90% and presenting the benchmarked results, it increased substantially to 97.5%. This could be associated with the increase of patients being discussed in a preoperative MDT meeting.

In contrast, the discrepancy between the cTNM and pTNM increased, with potential inferior (preoperative) treatment.[25] In 2014, a quality indicator was initiated to evaluate the increase of this discrepancy, and the effect is still being monitored.
Fewer irradical resections (R1/R2) were reported in 2013 to 2014, although in 2015 a slight increase in the rate was shown. A possible explanation is the cardiothoracic surgeons joined in 2015 and might have treated more patients with extensive and centrally located NSCLC. Overall, no statistically significant differences in outcomes between GTLs and CTSs were found. Compared with publications from other countries (3.3% to 12%), irradical resection rate is low, although indicator results depend on the quality of the operation and the quality of pathologic evaluation of resection margins.[26]
Short-term outcomes were not substantially different between the two specialties and did not change substantially during the study period, although a 30-day or in-hospital mortality rate between 1.5% and 2.9% can be considered an adequate result compared with the reported European 30-day mortality of 2.7% (range: 2% to 4.2%) and approximately 3% described by data from the UK National Lung Cancer Association.[27] Jakobsen and colleagues[6] described a decrease of 30-day mortality from 5.2% to 3.6% and a benefit in 1-, 2- and 5-year survival in patients who underwent operation during the period 2000 to 2006 in the Danish Lung Cancer Registry. The unexpected increase of severe complications from 11.7% to 15.5% in 2015 is currently subject of additional research.

**Limitations**

First, the DLSA data set contains many data points concerning all phases of treatment for reliable measurement and comparison. This is associated with a substantial administrative burden, because surgeons are responsible for their own data entry. Nevertheless, the data set is limited and needs careful evaluation on a yearly base to prevent adverse growth of the data set and to maintain suitability within clinical practice. In addition, synoptic reporting is developed for automatized connection and data transfer between several data sources to decrease registration burden and to increase data quality and reliability.
Besides administrative weight, data fraud is a potential adverse effect. Therefore, an independent third party visits hospitals and produces discrepancy reports based on their hospital data. Hospitals receive the report and use it to improve the quality of data entry by their lung surgeons

or trained administrative personnel.[28] The last verification in 2016 describes data completeness of 99.4% without under registration of mortality and complications. A third limitation concerns the content of the DLSA. From the start, the audit aimed particularly on general lung operations with a focus on NSCLC. Besides children, patients undergoing thymectomy or lung transplantation cannot be registered yet in the DLSA.

**Future perspectives**

The DLSA was designed with the idea that registering clinical information is not sufficient to give a total view of the outcomes of the treatment of lung cancer. Functional outcomes of patients after major pulmonary operation are considered important, especially with the poor prognosis of more extensive disease and the increase in elderly patients treated for lung cancer. A pilot will be started to register patient reported outcomes measures by patient themselves in a web-based environment. The questionnaires chosen by the International Consortium for Healthcare Outcomes Measurement will be used.[29] These data will be linked to the clinical information in DLSA, allowing risk-adjustment and segmentation of patient outcomes. In January 2016, the DLSA led to initiation of a multidisciplinary database: the Dutch Lung Cancer Audit. This new database will record the pathway of patients with lung cancer from diagnosis by the pulmonologist/oncologist until definite treatment and long- term follow-up. In the future, this unique registry will collaborate international lung cancer registries for international benchmarking.



## CONCLUSIONS

The DLSA shows increased participation and quality improvements in lung cancer operations in the Netherlands after the first 4 years, because of the central role of the medical specialists, high-quality data, and timely, online feedback of benchmarked results.

**TABLE 1.** Tumor and treatment characteristics of patients with non-small cell lung cancer and parenchymal resection (pneumonectomy, (bi)lobectomy, anatomical resection) in the Dutch Lung Surgery Audit by year

| | | 2012 | | 2013 | | 2014 | | 2015 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % | p[5] |
| **Age** | < 70 years | 823 | 63.7 | 1,016 | 62.2 | 989 | 63.6 | 1,220 | 62.6 | 0.210 |
| | ≧ 70 years | 472 | 36.6 | 617 | 37.8 | 567 | 36.4 | 729 | 37.3 | |
| **Sex** | Male | 720 | 55.8 | 937 | 57.4 | 872 | 56 | 1,083 | 55.6 | 0.566 |
| | Female | 575 | 44.5 | 696 | 42.6 | 684 | 44 | 866 | 44.4 | |
| **ASA** | I - II | 961 | 74.4 | 1,216 | 74.5 | 1,140 | 73.3 | 1,398 | 71.7 | 0.051 |
| | III+ | 292 | 22.6 | 398 | 24.4 | 385 | 24.7 | 473 | 24.3 | |
| | Missing | 42 | 3.3 | 19 | 1.2 | 31 | 24.7 | 78 | 4.0 | |
| **PET-CT scan** | No | 27 | 2.1 | 19 | 1.2 | 28 | 1.8 | 32 | 1.6 | |
| | Yes | 1,256 | 97.3 | 1,610 | 98.6 | 1,523 | 97.9 | 1,909 | 97.9 | 0.149 |
| | Missing | 12 | 0.9 | 4 | 0.2 | 5 | 0.3 | 8 | 0.4 | |
| **Endoscopic ultrasound** | No | 1,143 | 88.5 | 1,474 | 90.3 | 1,373 | 88.2 | 1,787 | 91.7 | 0.045 |
| | Yes | 112 | 8.7 | 126 | 7.7 | 131 | 8.4 | 144 | 7.4 | |
| | Missing | 40 | 3.1 | 33 | 2.0 | 52 | 3.3 | 18 | 0.9 | |
| **Endobronchial ultrasound** | No | 1,062 | 82.3 | 1,326 | 81.2 | 1,247 | 80.1 | 1,439 | 73.8 | 0.004 |

**TABLE 1.** Continued

| | | 2012 | | 2013 | | 2014 | | 2015 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % | p[§] |
| | Yes | 196 | 15.2 | 287 | 15.6 | 271 | 17.4 | 494 | 25.3 | |
| | Missing | 37 | 2.9 | 20 | 1.2 | 38 | 2.4 | 16 | 0.8 | |
| **Mediastinoscopy** | No | 967 | 74.9 | 1,184 | 72.5 | 1,177 | 75.6 | 1,500 | 77 | 0.04 |
| | Yes | 307 | 23.8 | 435 | 26.3 | 353 | 22.7 | 435 | 22.3 | |
| | Missing | 21 | 1.6 | 14 | 0.9 | 26 | 1.7 | 14 | 0.7 | |
| **Clinical stage** | Occult / 0 | 21 | 1.6 | 29 | 1.8 | 28 | 1.8 | 19 | 1.0 | 0.075 |
| | Stage I | 596 | 46.2 | 928 | 56.8 | 902 | 58 | 1,002 | 51.4 | |
| | Stage II | 244 | 18.9 | 384 | 23.5 | 386 | 24.8 | 553 | 28.4 | |
| | Stage IIIa | 65 | 5.0 | 135 | 8.3 | 134 | 8.6 | 212 | 10.9 | |
| | Stage IIIb | 5 | 0.4 | 20 | 1.2 | 12 | 0.8 | 18 | 0.9 | |
| | Stage IV | 12 | 0.9 | 17 | 1.0 | 9 | 0.6 | 17 | 0.9 | |
| | Missing | 352 | 27.3 | 120 | 7.4 | 85 | 5.5 | 128 | 6.6 | |
| **Induction therapy** | No | 1,198 | 92.8 | 1,518 | 93 | 1,427 | 91.7 | 1,811 | 92.9 | 0.588 |
| | Chemotherapy | 35 | 2.7 | 41 | 2.5 | 35 | 2.3 | 33 | 1.7 | |
| | Radiotherapy | 5 | 0.4 | 5 | 0.3 | 5 | 0.3 | 9 | 0.5 | |

**TABLE 1.** Continued

| | | 2012 | | 2013 | | 2014 | | 2015 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % | p[§] |
| | Chemoradiotherapy | 48 | 3.7 | 59 | 3.6 | 82 | 5.3 | 93 | 4.8 | |
| | Biologicals | 1 | 0.01 | 3 | 0.2 | 0 | 0 | 0 | 0 | |
| | Other | 2 | 0.2 | 3 | 0.2 | 4 | 0.3 | 1 | 0.1 | |
| | Missing | 6 | 0.5 | 4 | 0.2 | 3 | 0.2 | 2 | 0.1 | |
| **Resection type** | Pneumonectomy | 114 | 8.8 | 130 | 8 | 115 | 7.4 | 169 | 8.7 | 0.001 |
| | Bilobectomy | 77 | 63.7 | 103 | 6.3 | 108 | 6.9 | 114 | 5.8 | |
| | Lobectomy | 1,083 | 83.9 | 1,378 | 84.4 | 1,280 | 82.3 | 1,628 | 83.5 | |
| | Segmental resection | 21 | 1.6 | 22 | 1.3 | 53 | 3.4 | 38 | 1.9 | |
| **Pathological stage** | Occult / 0 | 25 | 1.9 | 21 | 1.3 | 29 | 1.9 | 41 | 2.1 | 0.547 |
| | Stage I | 646 | 50 | 845 | 51.7 | 783 | 50.3 | 919 | 47.2 | |
| | Stage II | 325 | 25.1 | 413 | 25.3 | 388 | 25 | 536 | 27.5 | |
| | Stage IIIa | 141 | 10.9 | 198 | 12.1 | 188 | 12.1 | 288 | 14.8 | |
| | Stage IIIb | 5 | 0.4 | 9 | 0.6 | 2 | 0.1 | 8 | 0.4 | |
| | Stage IV | 12 | 0.9 | 17 | 1.0 | 12 | 0.8 | 27 | 1.4 | |
| | Missing | 141 | 10.9 | 130 | 8 | 154 | 9.9 | 130 | 6.7 | |

**TABLE 1.** Continued

| | | 2012 | | 2013 | | 2014 | | 2015 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % | p[§] |
| **Adjuvant therapy** | No | 2 | 0.2 | 5 | 0.3 | 9 | 0.6 | 1,268 | 65.1 | 0.717 |
| | Chemotherapy | 2 | 0.2 | 1 | 0.1 | 2 | 0.1 | 451 | 23.1 | |
| | Radiotherapy | 0 | 0 | 0 | 0 | 2 | 0.1 | 55 | 2.8 | |
| | Chemoradiotherapy | 0 | 0 | 0 | 0 | 0 | 0 | 86 | 4.4 | |
| | Biologicals | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.1 | |
| | Other | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 0.5 | |
| | Missing | 1,291 | 99.6 | 1,627 | 99.6 | 1,543 | 99.2 | 77 | 4 | |

ASA: American Society of Anesthesiologists
§ $\chi 2$ test for trend

**TABLE 2.** Quality Indicator for Lung Carcinoma in the Netherlands

| Indicatortype | Description | 2012 | 2013 | 2014 | 2015 | |
|---|---|---|---|---|---|---|
| **Structure** | | n | n | n | n | p[§] |
| 1. | Volume | | | | | |
| | Number of patients with lung resection for non-small cell lung cancer | 1,478 | 1,871 | 1,765 | 2,281 | |
| | Number of patients with mediastinoscopy | 668 | 794 | 868 | 1,051 | |
| | Number of patients with metastasectomy | 250 | 333 | 356 | 420 | |
| | Number of patiens with non malignant thorax operation | 1,377 | 1,792 | 1,817 | 2,436 | |
| 2. | Number of patients with anatomical lung parenchymal resection | 1,419 | 1,800 | 1,725 | 2,290 | |
| **Process** | | % | % | % | % | |
| 3. | Percentage of non-small cell lung cancer patients discussed in MDT meeting *before* lung operation | 81.5 | 91.6 | 96.8 | 96.5 | 0.001 |
| 4. | Percentage of non-small cell lung cancer patients with *clinical* TNM stage recorded *before* undergoing lung operation | 74.3 | 95.4 | 96.5 | 93 | 0.001 |
| 5. | Percentage of non-small cell lung cancer patients with *pathological* TNM stage recorded *after* undergoing lung operation | 97.5 | 98 | 98.5 | 99 | 0.061 |
| 6. | Percentage of non-small cell lung cancer patients with discrepancy between clinical and pathological TNM stage after undergoing lung operation | 59.3 | 50.5 | 52.5 | 54.5 | 0.001 |

**TABLE 2.** Continued

| Indicatortype | Description | 2012 | 2013 | 2014 | 2015 | |
|---|---|---|---|---|---|---|
| 7. | Percentage of non-small cell lung cancer patients with maximal lead time of 21 days between the last MDT meeting and lung operation | 40.8 | 57.9 | 62.2 | 64.1 | 0.001 |
| **Outcome** | | % | % | % | % | |
| 8. | Percentage of non-small cell lung cancer patients with a 30-day mortality after lung operation | 2.9 | 1.5 | 2.6 | 2 | 0.303 |
| 9. | Percentage of non-small cell lung cancer patients with a severe complication after lung operation* | 13.7 | 11.8 | 11.8 | 15.5 | 0.788 |
| 10. | Percentage of non-small cell lung cancer patients with an irradical resection (R1 or R2) after lung operation | 6.5 | 5.5 | 5.5 | 6.3 | 0.441 |

MDT: multi disciplinary team; TNM: TNM seventh Edition

* Severe complications: postoperative course concerning 30-day mortality; ICU stay > 3 days; reintervention (bronchoscopy, interventional radiology, redo surgery); or length of stay >14 days.

[§] Determined by $\chi^2$ test for trend

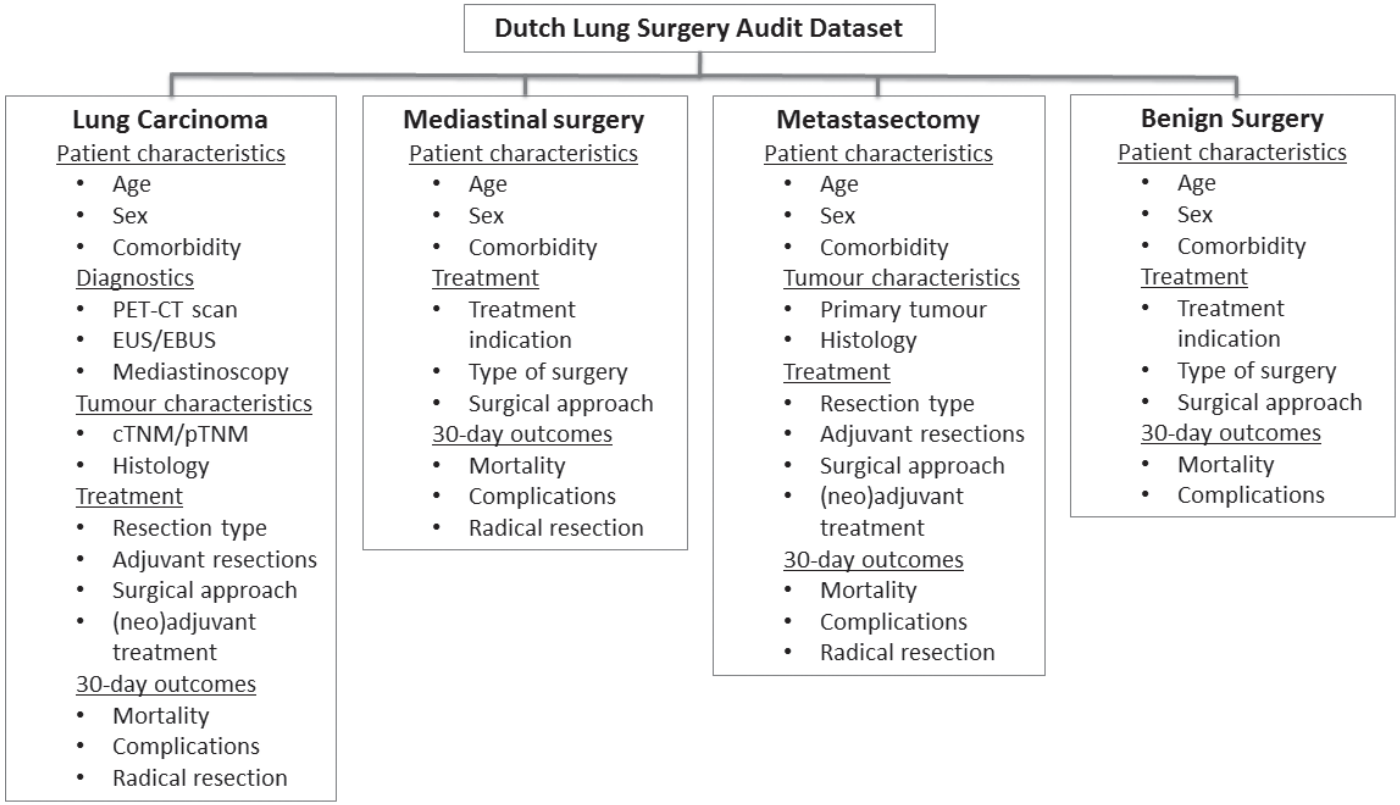


**FIGURE 1.** Diagram representing the data set of the Dutch Lung Surgery Audit (DLSA). (EUS/EBUS = endoscopic ultrasound/endobronchial ultrasound; PET-CT = positron emission tomography computed tomography)

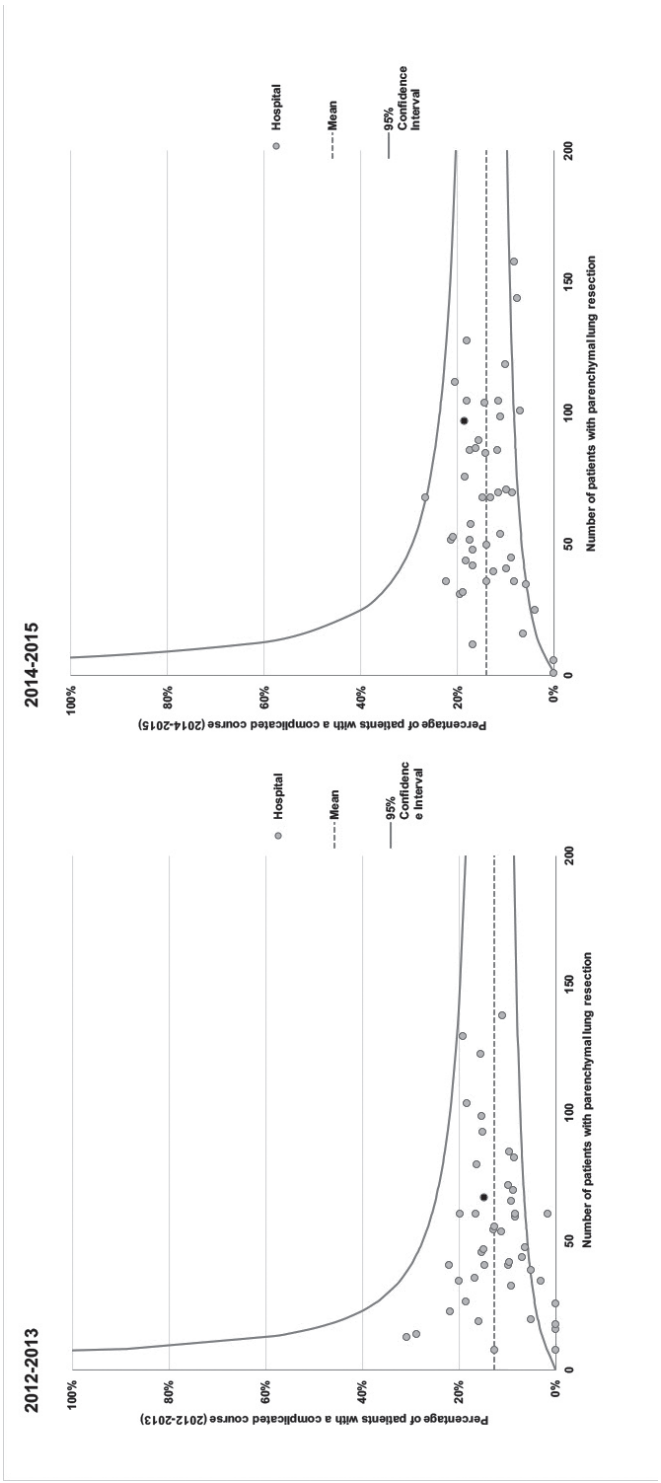


**FIGURE 2.** Example of funnel plots presenting results of the quality indicator "Percentage of patient with a severe complication after pulmonary resection (case-mix corrected)" displayed at MyDLSA. Black dot indicates your hospital.

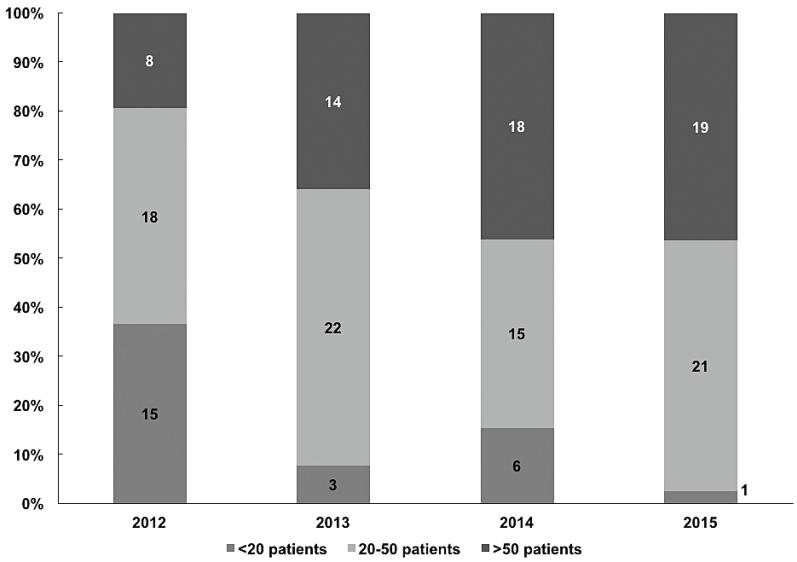


**FIGURE 3.** Diagram representing volume groups of parenchymal (pneumonectomy, (bi)lobectomy or segmental) resection in the period 2012 to 2015. The number in the bar gives the absolute number of hospitals in the volume group.

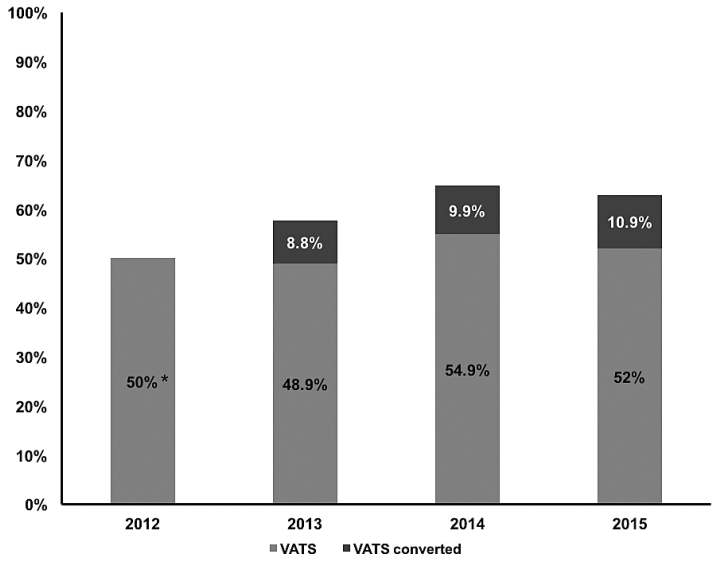


**FIGURE 4.** Percentage of parenchymal resections performed with video-assisted thoracic surgery (VATS). *VATS conversion was not registered in 2012.

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# THE QUALITY OF STAGING NON-SMALL CELL LUNG CANCER IN THE NETHERLANDS

3

## DATA FROM THE DUTCH LUNG SURGERY AUDIT

*Ann Thorac Surg. 2016;102:1622-9.*

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## ABSTRACT

### Background

Clinical staging of non-small cell lung cancer (NSCLC) determines the initial treatment offered to a patient. The similarity between clinical and pathologic staging in some studies is as low as 50%, and others publish results as high as 91%. The Dutch Lung Surgery Audit is a clinical database that registers the clinical and pathologic TNM of almost all NSCLC patients who undergo operations in the Netherlands. The objective of this study was to determine the accuracy of clinical staging of NSCLC.

### Methods

Prospective data were derived from the Dutch Lung Surgery Audit in 2013 and 2014. Patients were included if they had undergone a surgical resection for stage IA to IIIB NSCLC without neoadjuvant treatment and had a positron emission tomography–computed tomography scan as part of the clinical workup. Clinical (c)TNM and pathologic (p)TNM were compared, and whether discrepancy was based on tumor or nodal staging was determined.

### Results

From 2,834 patients identified, 2,336 (82.4%) fulfilled the inclusion criteria and had complete data. Of these 2,336, 1,276 (54.6%) were staged accurately, 707 (30.3%) were clinically understaged, and 353 (15.1%) were clinically overstaged. In the understaged group, 346 patients had a higher pN stage (14.8%), of which 148 patients had unforeseen N2 disease (6.3%). In the overstaged group, 133 patients had a cN that was higher than the pN (5.7%).

### Conclusions

Accuracy of NSCLC staging in the Netherlands is low (54.6%), even in the era of positron emission tomography–computed tomography. Especially accurate nodal staging remains challenging. Future efforts should include the identification of specific pitfalls in NSCLC staging.

## INTRODUCTION

Lung cancer staging involves a complex multidisciplinary process in which a specific combination of imaging modalities, minimally invasive staging procedures, or invasive staging procedures are selected for the individual patient to achieve accurate stage information with the lowest possible patient burden.[1,2] In May 2013 the journal Chest published a supplement, "Methods for staging non-small cell lung cancer," an evidence- based clinical practice guideline by the American College of Chest Physicians. The authors of this guideline conducted a thorough review of the literature, and from that review they proposed a diagnostic work-up for patients suspected of non-small cell lung cancer (NSCLC) to assure accurate clinical (c)TNM staging. This staging routinely comprises a positron emission tomography (PET)–computed tomography (CT) scan, if available, and otherwise a CT scan. In case of a suspicious mediastinal node on the PET-CT, minimally invasive techniques, such as endoscopic ultrasound (EUS) and endobronchial ultrasound (EBUS), or a surgical biopsy (mediastinoscopy) are advised to stage the mediastinum. In patients with an intermediate risk for N2 or N3 involvement, with a central tumor or N1 lymph node involvement, invasive staging of the mediastinum is also recommended. Magnetic resonance imaging of the brain is recommended in patients with clinical stage III disease. Although data are published regarding the sensitivity and specificity of the different diagnostic modalities, the accuracy of the diagnostic process as a whole was not described in this publication of the American College of Chest Physicians.[2]

The available studies on the individual staging techniques often had a retrospective design and a small sample size, which precludes robust conclusions. The accuracy of clinical staging is generally low, at approximately 50% to 60%.[3-8] A recent study from Denmark showed an increase in the accuracy of the staging process from 68% to 91% in the last 10 years, possibly due to centralization of lung cancer care during this period.[9]

The introduction of the PET-CT scan in the diagnostic work-up is also thought to benefit the accuracy of the full staging process, although little is known about this effect because most studies looking at the accuracy of staging date from the era before PET-CT. PET was introduced in the Netherlands in 1991 but was only widely used after 2007.[10] Part of the improvement seen in the Danish study might also be due to introduction of the PET-CT scan. A high correlation between the cTNM and pathologic (p)TNM staging is considered very important, because inaccurate staging may cause

undertreatment or overtreatment of patients, especially with the recent introduction of stereotactic ablative radiotherapy in early-stage lung cancer and induction therapy for stage IIIA tumors. Furthermore, the correlation between cTNM and pTNM is also an important indicator of the quality of the total diagnostic setup.[9]

The main objective of this study was to assess the real-world accuracy of the staging process by evaluating discrepancies between cTNM and pTNM staging in a national database including patients who underwent surgical resection for NSCLC in the Netherlands.

## MATERIAL AND METHODS

### Data source

The study used data from the Dutch Lung Surgery Audit (DLSA), a nationwide clinical registry used for evaluation of quality of care for benign and malignant lung operations. Information on patient characteristics, diagnostics, tumor characteristics, treatment, and outcomes has been recorded prospectively since 2012. The quality of this database is regularly checked, for example, by comparing the data with the Netherlands Cancer Registry, a database with data on the incidence, prevalence, survival, and death of all cancer types.[11] Completeness and data consistency of the DLSA is checked through queries, with results given as feedback to individual hospitals and requests to check any inconsistencies that are identified by these queries.

### Patients

The study evaluated data for all patients who underwent anatomical parenchymal (pneumonectomy, [bi]lobectomy, or sublobar) lung resections between January 1, 2013, and December 31, 2014, and were registered in the DLSA. Minimal data requirements for inclusion in the analysis were information on cTNM and pTNM stage, type of parenchymal resection, and the histopathologic determination. Patients who presented with acute symptoms, other histopathology than NSCLC, stage IV lung cancer, neoadjuvant treatment, or no PET-CT scan were excluded.

### Outcome

The primary outcome was accurate clinical staging, using the pTNM stage (The TNM Classification of Malignant Tumours, 7th Edition) as the gold

standard. When cTNM stage was lower than pTNM stage this was considered as understaging, regardless of the extent of understaging (eg, 1A vs 1B or 1A vs 2A). Secondary outcomes were the number of misdiagnosed patients based on N and T stage. Patients misdiagnosed on both the N and T stage were placed in the N stage group because clinical consequences for inaccurate N staging were generally more important than for inaccurate T staging.

The use of invasive diagnostics, such as EUS, EBUS, and (video) mediastinoscopy, was investigated in suspicious nodes (enlarged [short axis of diameter >1 cm] or PET-positive) to analyze the adherence to guidelines on staging mediastinal lymph nodes. This was done by analyzing the results of negative invasive diagnostic studies in suspicious nodes that were pathologically reviewed. Because an accurate lymph node dissection or sampling is mandatory to provide correct pTNM staging, we analyzed the lymph node stations that were dissected or sampled.



**Statistical analysis**

As a first step, we compared included with excluded patients on a number of preoperative patient characteristics and the clinical stage to be able to assess the generalizability of our results (selection bias). This was done using Chi-square tests and the Fisher exact test when expected counts were less than 5.

Secondly, we compared the clinical and pathologic stage of the included patients and estimated the accuracy for each clinical stage. Then we compared patients with accurate staging with patients with inaccurate staging on age, sex, performance score, comorbidities, previous thoracic operations, clinical stage, and tumor side using Chi-square tests for categoric variables and t tests for continuous variables.

As a final step, all variables significantly associated with inaccurate staging in univariate analysis were entered in a multivariate logistic regression analysis with inaccurate staging (yes/no) as the dependent variable. Statistical analysis was performed in PASW Statistics 21 (IBM Corp, Armonk, NY), and a p-value smaller than 0.05 was considered statistically significant in all analyses.

## RESULTS

### Demographics and risk factors

From January 1, 2013, to December 31, 2014, 2,834 eligible patients underwent anatomical parenchymal resection for NSCLC from 38 hospitals in the Netherlands, and 2,336 (82.4%) were included. Figure 1 shows a flow chart of inclusion and reasons for exclusion. Patient and tumor characteristics of included and excluded patients are reported in Table 1. Included patients were significantly older and had more cardiac comorbidity and fewer previous thoracic operations.

### Discrepancy between cTNM and pTNM

A total of 1,276 patients (54.6%) were staged accurately, 707 (30.3%) patients were clinically understaged, and 353 (15.1%) were clinically overstaged. Table 2 reports the accuracy for each clinical stage, from 40.2% for IIA to 66.7% for IA. To assess which patients were staged accurately, we compared accurately and inaccurately staged patients. Table 3 reports the results from the multivariate analysis, which showed that accuracy of staging is better in patients with a previous thoracic operation, early-stage NSCLC, and in women.

### Discrepancy based on clinical tumor and lymph node status

Figure 2 shows a subanalysis of cT and cN stage. Of the 707 patients clinically understaged, 353 (15.1%) had a higher pT stage than expected, and 346 patients had a higher pN stage (14.8%). In this group, 148 patients (6.3% of total study population) had unforeseen N2 nodes. Eight patients were understaged because of the combination of a higher pT stage, but a lower pN stage; for example cT2a N1 (stage IIA) to pT3 N0 (stage IIB), and these were placed in the "other" group.

When looking at the 353 patients in the clinically overstaged group, 209 (8.9%) had a lower pT stage than expected and 133 (5.7%) a lower pN stage. Eleven patients were in the "other" group, meaning they were overstaged based on a cT stage that was too high and cN stage that was too low; for example cT3 N0 (stage IIB) to pT2a N1 (stage IIA).

### Analysis of mediastinal staging

Table 4 reports an analysis of suspicious mediastinal lymph nodes in the entire population of 2,336 patients. The analysis shows whether a lymph node station was enlarged or positive, or both, on the PET-CT scan and the

types of invasive diagnostics that were used. Only nodes with a negative invasive diagnostic workup are reported. Of 711 lymph node stations that were suspicious on PET-CT, 617 lymph node stations were evaluated with invasive di- agnostics (EUS, EBUS, mediastinoscopy, or a combination of these) that gave a negative result. After the operation and pathologic review, 232 of 711 (32.6%) of these suspicious lymph node stations proved positive for tumor.

**Tumor resection and lymph node dissection or sampling**

Because an accurate lymph node dissection is mandatory to provide a correct pTNM stage we analyzed the lymph node stations that were dissected or sampled. As reported in Table 5, lobectomy of the right upper lobe was the procedure performed most frequently (699 patients). Lymph node station N7 was dissected/sampled most frequently in addition to the different types of parenchymal resection (1,726 of 2,336). No details were available on how many nodes were harvested per station.



## COMMENT

Accuracy of staging NSCLC can be considered low in the Netherlands. This study shows accurate staging of 54.6% in a cohort of 2,336 patients, with 30.3% of the patients being clinically understaged and 15.1% clinically overstaged. Accuracy of staging is significantly higher in early-stage lung cancer, women, and patients with previous thoracic operations. Nodal staging is difficult, resulting in 479 patients with an inaccurate clinical stage based on nodes and 6.3% of patients having unforeseen N2 disease.

Multiple studies in the last 20 years have described the difficulty in reliable staging of lung cancer. Accuracy ranges from 35% to 91% and seems higher in the lower clinical stages. Most of these studies were published in the era before PET-CT, but the present study shows that accuracy is still better in patients with lower clinical stages.[3-9] Accurate staging is becoming increasingly important with clinical consequences, especially with the recent introduction of stereotactic ablative radiotherapy in early-stage lung cancer and induction therapy for stage IIIA tumors.

Only the Danish group, who had moderate accuracy at best in the past, recently reported high rates of accuracy. Jakobsen and colleagues[9] published a high rate of 91.3% accuracy between cTNM and pTNM in 2012 in Denmark with data from the Danish Lung Cancer Registry. They report an

improvement of accuracy of 68.2% to 91.3% in 10 years (2003 to 2012). It is important to mention that they only reported inaccuracy if this had clinical consequences (cT1-3 to pT4 and cN0-1 to pN2-3 or cN2 to pN3). Theirs is a more liberal definition of accuracy than used in this report, where every clinical stage has been compared with the pathologic stage and thus likely to partly explain the lower percentage found in the present study. Their study emphasizes that an inaccurate cTNM classification is a problem for the individual patient and for health economics; hence, the degree of concordance between cTNM and pTNM is an important quality indicator for the diagnostic process. Interestingly, they also state that a high number of accurately staged patients will increase survival after the operation but probably not overall survival.

PET scanning is generally assumed to improve the diagnostic process of NSCLC. In a comparison with conventional imaging PET scanning makes understaging less likely (15% vs 30%).[12] The effect of PET scanning diminishes in patients with less extensive disease. An analysis of clinical stage I tumors in the American College of Surgeons Oncology group PET scanning study found that PET detected N2, N3, or M1 involvement in 7% of patients at a price of 14% false-positive N2, N3, or M1 results.[13] Because PET scanning carries a risk of inaccurate upstaging, histopathologic confirmation of positive lymph nodes or metastases is necessary before a patient is denied a possible curative resection.

**Concordance of cTNM and pTNM in this study**

We found concordant cTNM and pTNM in only 54.6% of the patients in our study. All 2,336 patients had a PET-CT scan as part of their diagnostic process and were staged according to the 7th Edition of the TNM Classification of Malignant Tumours (2010).[14] This corresponds with the current literature, although almost all of the literature that has been written about this subject dates from the pre-PET era.

It is remarkable that the accuracy is only 54.6%, with all diagnostic modalities available in the Netherlands, especially when the sensitivity and specificity of these modalities are all very high; for example, 91% sensitivity and 100% specificity for the combination of EUS and EBUS.[2] The article published by Jakobsen and colleagues[9] from the Danish Lung Cancer Registry shows a much higher concordance between cTNM and pTNM. Part of the explanation may be the more strict definition of accurate staging, as discussed above,

and the more rigorous centralization of lung cancer care (including staging) in Denmark might also be of importance.[9]

Our multivariate analysis showed female gender, previous thoracic operation, and lower clinical stage are factors that independently contribute to accurate staging. The effect of a previous thoracic operation might be the result of a higher awareness of false staging after a previous operation in the same area. Unfortunately, which exact previous thoracic procedure was performed in these patients is not recorded.

From our subanalysis on whether a patient is misdiagnosed by the tumor stage or nodal stage, nodal staging is particularly interesting because these patients could have benefitted from invasive diagnostic modalities to get an accurate clinical stage. When the numbers in Figure 2 are added, 20.5% of patients seem wrongly staged based on a discrepancy in their preoperative and postoperative nodal stage. In total, 24.1% of patients are misdiagnosed based on tumor stage.

Of the 711 suspicious lymph node stations, 617 had invasive diagnostics with a negative result and 232 were pathologically tumor positive. Why 94 lymph node stations were not analyzed preoperatively remains unclear: the DLSA does not provide data on this. The rate of unforeseen N2 nodes in this series is 6.3%, which is in accordance with current literature. Lowering this rate even more might be possible with increased use of invasive diagnostics preoperatively.

The DLSA does not record the completeness of dissection or sampling in each station, and the data show that most surgeons use lobe-specific lymph node dissection. Although level 7 should be dissected in every patient, this was done in 1,726 patients (73.9%). That 35 lymph node stations level 5 and 6 were recorded in right-sided tumors is remarkable: this is probably a result of registration error. A sublobar resection was performed in 53 patients, and whether the resection was left-sided or right-sided was not recorded.

**Limitations**

This study has several limitations. First the data are self-reported by doctors or specialized nurses, so bias could be introduced. However, the data are verified by an external organization and compared with the data in the Netherlands Cancer Registry to increase the reliability of outcomes. In addition the data set contains detailed prospective preoperative, postoperative, and histopathologic data, so accurately distinguishing a cT stage from a pT stage was possible.

Second, this study does not describe the long-term results of patients with an understaged or overstaged cTNM, so whether these patients suffer worse outcomes is still unclear.
Third, the pTNM stage was considered the gold standard in this study, being the stage after pathologic review of the specimen that was resected. This has its limitations though. Completeness of the mediastinal lymph node dissection can be a problem when determining the accuracy of pTNM: there is no consensus whether lymph node dissection should be complete to enhance survival or whether lymph node sampling is enough to determine a pathologic stage to guide decision making about adjuvant treatment. This might influence the accuracy of the pN stage. As we mentioned before, not all patients received a total lobe-specific node dissection, thus influencing accuracy of pTNM.
That CT scanning overestimates tumor size compared with pathologic review is well known in the literature. A study of early-stage lung cancer described a relative difference of 18.3% between CT scanning and measurements after resection. Reasons are an inflated lung when scanning, inflammation, infiltration, or edema.[15] In our opinion, overestimation or underestimation of tumor stage is not a major problem in staging lung cancer because this hardly determines whether a patient will undergo an operation. Infiltration of vital structures or lymph node metastasis does determine whether a patient is operated on though.
Finally, certain details are, unfortunately, not recorded in the DLSA. The position of a tumor in the lungs is not recorded, for example; hence, we cannot analyze whether a central tumor received correct (minimal) invasive diagnostics of the mediastinum. The amount of [18F]Fluorodeoxyglucose uptake on the PET-CT is not recorded; hence, we cannot make a comparison between uptake of the primary tumor and mediastinal uptake. The same is true for histopathologic proof of the primary tumor: we cannot analyze the number of specimen-proven patients and the extent to which this influences accurate clinical staging. Unfortunately, the process of certain decisions remains unclear, for example, the number of patients with clinical stage IIIA tumors (155) who received a resection without induction therapy.

**Implications of this study for clinical practice or future research**

This study shows underperformance of clinical staging of NSCLC in the Netherlands. How this affects patient survival and how the staging process can be improved requires additional and more detailed analyses. Because

the unforeseen N2 rate was 6.3% in this study, most progression is expected from better interpretation of the PET- CT, thus improving accuracy of cT and N1 stage. In 2016 the DLCA will start a multidisciplinary audit comprising all patients with lung cancer. With this audit we want to provide quality assurance of the staging process and audit the different lung cancer teams in the Netherlands.

## CONCLUSIONS

Accuracy of staging NSCLC in the Netherlands is low (54.6%), even in the era of PET-CT scans. Wrong interpretation of the PET-CT scan might be an important factor in inaccurate staging. Especially N1 nodal staging is often inaccurate, which may have important implications for the treatment offered to a patient. Guidelines for nodal staging and nodal dissection should be monitored closely. Future efforts should include the identification of specific pitfalls in NSCLC staging and assessment of the effect of inaccurate staging on patient outcome. Subsequent changes in lung cancer care will hopefully result in improved clinical staging and outcome.

**TABLE 1.** Baseline characteristics of included and excluded patients.

| | | Included | | Excluded | | |
|---|---|---|---|---|---|---|
| | | n | % | n | % | p |
| **Sex** | Male | 1,330 | 56.9 | 297 | 59.6 | 0.25 |
| | Missing | 0 | 0.0 | 1 | 0.2 | |
| **Age** | < 75 years | 1,835 | 78.6 | 434 | 87.1 | < 0.05 |
| | 75+ years | 490 | 21.0 | 60 | 12.0 | |
| | Missing | 11 | 0.5 | 4 | 0.8 | |
| **ECOG score** | ECOG 0 | 1,172 | 50.2 | 209 | 42.0 | < 0.05 |
| | ECOG 1 | 588 | 25.2 | 115 | 23.1 | |
| | ECOG 2 | 78 | 3.3 | 15 | 3.0 | |
| | ECOG 3 | 7 | 0.3 | 7 | 1.4 | |
| | ECOG 4 | 1 | 0.0 | 1 | 0.2 | |
| | Missing | 490 | 21.0 | 151 | 30.3 | |
| **Cardiac comorbidity** | No | 1,682 | 72.0 | 391 | 78.5 | < 0.05 |
| | Yes | 654 | 28.0 | 107 | 21.5 | |
| **Pulmonary comorbidity** | No | 1,467 | 62.8 | 329 | 66.1 | 0.17 |
| | Yes | 869 | 37.2 | 169 | 33.9 | |
| **Neurological comorbidity** | No | 2,001 | 85.7 | 436 | 87.6 | 0.27 |
| | Yes | 335 | 14.3 | 62 | 12.4 | |
| **Previous thoracic surgery** | No | 2,201 | 94.2 | 454 | 91.2 | < 0.05 |
| | Yes | 135 | 5.8 | 44 | 8.8 | |
| **Clinical Stage **** | 0 | 0 | 0.0 | 41 | 8.2 | < 0.05 |
| | IA | 995 | 42.6 | 52 | 10.4 | |
| | IB | 547 | 23.4 | 41 | 8.2 | |
| | IIA | 346 | 14.8 | 26 | 5.2 | |
| | IIB | 279 | 11.9 | 60 | 12.0 | |
| | IIA | 155 | 6.6 | 81 | 16.3 | |

**TABLE 1.** Continued

| | | Included | | Excluded | | |
|---|---|---|---|---|---|---|
| | | n | % | n | % | p |
| | IIIB | 14 | 0.6 | 18 | 3.6 | |
| | IV | 0 | 0.0 | 24 | 4.8 | |
| | Missing | 0 | 0.0 | 155 | 31.1 | |
| **Side of tumor** | Left | 993 | 42.5 | 215 | 43.2 | 0.82 |
| | Right | 1,332 | 57.0 | 282 | 56.6 | |
| | Missing | 11 | 0.5 | 1 | 0.2 | |

* Analyzed by Chi-square test
** Clinical stage according to TNM 7th edition

ECOG = Eastern Cooperative Oncology Group

**TABLE 2.** Accuracy of clinical staging, using pathological stage as the gold standard

| | | **pStage** | | | | | | **Total** | **Accurate staging (%)** |
|---|---|---|---|---|---|---|---|---|---|
| | | Stage IA | Stage IB | Stage IIA | Stage IIB | Stage IIIA | Stage IIIB | | |
| **cStage** | Stage IA | 664 | 181 | 67 | 25 | 57 | 1 | 995 | 66.7 |
| | Stage IB | 79 | 267 | 108 | 40 | 53 | 0 | 547 | 48.8 |
| | Stage IIA | 43 | 58 | 139 | 54 | 48 | 4 | 346 | 40.2 |
| | Stage IIB | 22 | 27 | 44 | 119 | 66 | 1 | 279 | 42.7 |
| | Stage IIIA | 13 | 11 | 17 | 25 | 87 | 2 | 155 | 56.1 |
| | Stage IIIB | 2 | 2 | 3 | 3 | 4 | 0 | 14 | 0.0 |
| **Total** | | 823 | 546 | 378 | 266 | 315 | 8 | 2,336 | |

cStage – clinical stage
pStage – pathological stage

**TABLE 3.** Multivariate analysis of the risk for discordance in clinical and pathological stage after resection for NSCLC.

| | | Univariate | | | | Multivariate | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | OR | Confidence interval | | | OR | Confidence interval | | |
| | | | 95% low | 95% high | p | | 95% low | 95% high | p |
| **Age (<75 yrs; ref)** | ≥ 75 yr | 0.924 | 0.765 | 1.116 | 0.575 | | | | |
| **Sex (male; ref)** | Female | 0.728 | 0.618 | 0.858 | <0.05 | 0.822 | 0.692 | 0.976 | p<0.05 |
| **ASA score (1-II; ref)** | III+ | 0.895 | 0.739 | 1.085 | 0.260 | | | | |
| **Cardial comorbidity (no; ref)** | Yes | 0.964 | 0.804 | 1.154 | 0.688 | | | | |
| **Pulmonary comorbidity (no; ref)** | Yes | 1.016 | 0.859 | 1.201 | 0.856 | | | | |
| **FEV1 (> 40%; ref)** | < 40% | 1.642 | 0.799 | 3.371 | 0.119 | | | | |
| | Missing | 0.917 | 0.762 | 1.304 | 0.596 | | | | |
| **DLCO (> 40%; ref)** | < 40% | 1.187 | 0.577 | 2.442 | 0.878 | | | | |
| | Missing | 0.929 | 0.766 | 1.126 | 0.774 | | | | |
| **Previous thoracic surgery (no; ref)** | Yes | 0.584 | 0.406 | 0.841 | <0.05 | 0.608 | 0.418 | 0.886 | p<0.05 |
| **Clinical Stage (IA; ref)** | IB | 2.137 | 1.728 | 2.642 | <0.05 | 1.971 | 1.587 | 2.447 | p<0.05 |
| | IIA | 2.949 | 2.295 | 3.792 | <0.05 | 2.652 | 2.048 | 3.435 | p<0.05 |
| | IIB | 2.695 | 2.057 | 3.532 | <0.05 | 2.378 | 1.798 | 3.144 | p<0.05 |
| | IIIA | 1.575 | 1.12 | 2.216 | <0.05 | 1.36 | 0.955 | 1.938 | 0.88 |
| | IIIB | 1 | 1 | . | 0.998 | | | | |
| **Tumor side (left; ref)** | Right | 0.989 | 0.839 | 1.165 | 0.895 | | | | |

**TABLE 3.** Continued

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **EUS (no; ref)** | Yes | 1.452 | 1.07 | 1.969 | <0.05 | 0.861 | 0.626 | 1.184 | 0.356 |
| **EBUS (no; ref)** | Yes | 1.388 | 1.121 | 1.72 | <0.05 | 0.922 | 0.734 | 1.159 | 0.488 |
| **Mediastinoscopy (no; ref)** | Yes | 1.657 | 1.372 | 2.001 | <0.05 | 0.813 | 0.66 | 1.001 | 0.051 |
| | | | | | $R^2$ Nagelkerke | 0.085 | | | |

ASA = American Society of Anaesthesiologists
CI = confidence interval
DLCO = diffusion capacity of the lung for carbon monoxide
EBUS = endobronchial ultrasound
EUS = endoscopic ultrasound
FEV1 = forced expiratory volume in 1 second
OR = odds ratio
ref = reference

**TABLE 4.** Analysis of suspicious mediastinal lymph node stations, staging techniques and their pathological outcome

| Lymph node station | Pre-op lymph node enlarged and/or PET-positive | Evaluated with invasive diagnostics | Negative EUS | Negative EBUS | Negative (video) mediastinoscopy | Pathology post-op pos |
|---|---|---|---|---|---|---|
| 2L | 20 | 16 | 6 | 9 | 11 | 1 |
| 2R | 69 | 61 | 13 | 37 | 44 | 12 |
| 3 | 20 | 15 | 2 | 6 | 12 | 1 |
| 4L | 100 | 90 | 25 | 44 | 74 | 5 |
| 4R | 221 | 199 | 32 | 116 | 154 | 48 |
| 5 and/or 6 | 103 | 82 | 22 | 34 | 61 | 72 |
| 7 | 153 | 134 | 44 | 71 | 94 | 61 |
| 8 | 15 | 12 | 6 | 1 | 7 | 16 |
| 9 | 10 | 8 | 4 | 1 | 6 | 16 |
| Total | 711 | 617 (86.8%) | 154 (21.7%) | 319 (44.9%) | 463 (65.1%) | 232 (32.6%) |

EBUS = endobronchial ultrasound
EUS = endoscopic ultrasound
PET = positron emission tomography
Post-op = postoperative
Pre-op = preoperative

**TABLE 5.** Type of resection and lymph node dissection/sampling

| Procedure | | Lymph node stations dissected/sampled | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 5 / 6 | 7 | 8 | 9 |
| RUL lobectomy | 699 | 386 | 17 | 573 | 24 | 547 | 155 | 142 |
| RML lobectomy | 90 | 37 | 0 | 56 | 2 | 61 | 20 | 23 |
| RLL lobectomy | 315 | 67 | 4 | 139 | 4 | 269 | 169 | 178 |
| Right pneumonectomy | 67 | 28 | 1 | 21 | 4 | 59 | 33 | 29 |
| Bilobectomy RUL/RML | 75 | 5 | 2 | 55 | 0 | 50 | 15 | 14 |
| Bilobectomy RML/RLL | 74 | 53 | 6 | 31 | 1 | 69 | 41 | 42 |
| LUL lobectomy | 295 | 27 | 2 | 76 | 509 | 384 | 124 | 197 |
| LLL lobectomy | 567 | 7 | 20 | 27 | 139 | 216 | 141 | 203 |
| Left pneumonectomy | 101 | 7 | 1 | 72 | 88 | 71 | 43 | 63 |
| Other | 53 | | | | | | | |
| Total | 2,336 | 617 26.4% | 53 2.3% | 1,050 44.9% | 771 33.0% | 1,726 73.9% | 741 31.7% | 891 38.1% |

LLL = left lower lobe
LUL = left upper lobe
RLL = right lower lobe
RML = right middle lobe
RUL = right upper lobe

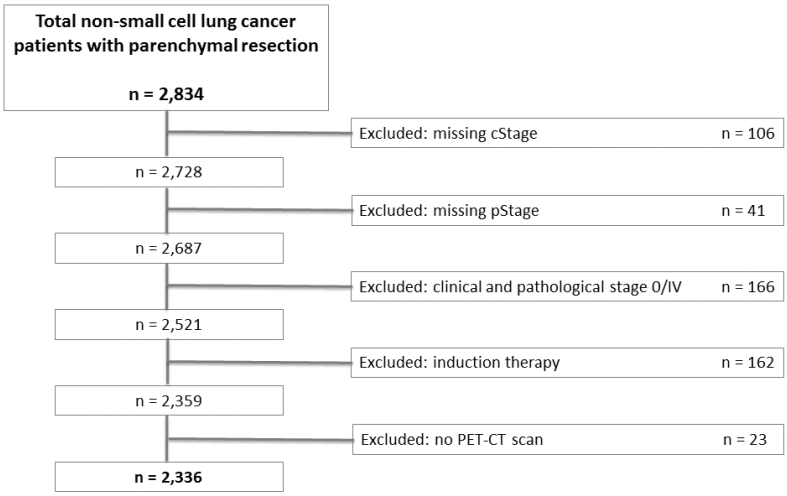


**FIGURE 1.** Flowchart of included and excluded patients

cStage = clinical stage
pStage = pathological stage
PET-CT = positron emission tomography-computed tomography

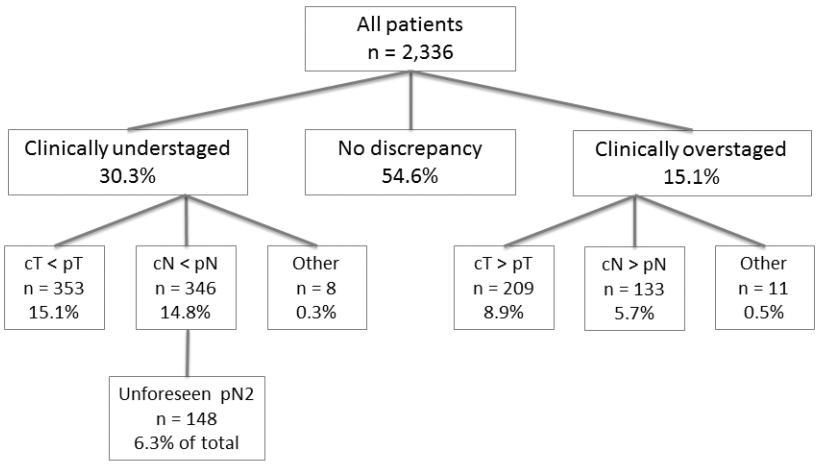


**FIGURE 2.** Flowchart describing the understaged and overstaged group based on over- or underestimated cT or cN. Only patients who changed from stage group were taken into account. The "other" understaged group comprises patients who switched stage based on a larger T, but have a smaller pN stage (for example: cT2aN1 to pT3N0 is a switch from stage IIA to IIB). In the "other" overstaged group this is the other way around.

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# 4

# CLINICAL STAGING OF STAGE I NON-SMALL CELL LUNG CANCER IN THE NETHERLANDS - NEED FOR IMPROVEMENT IN AN ERA WITH EXPANDING NONSURGICAL TREATMENT OPTIONS.

## DATA FROM THE DUTCH LUNG SURGERY AUDIT

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## ABSTRACT

### Background

The clinical stage of non-small cell lung cancer (NSCLC) determines the initial treatment, whereas the pathologic stage best determines prognosis and the need for adjuvant treatment. In an era in which stereo- tactic ablative radiotherapy (SABR) has become an alternative modality to surgical intervention, clinical staging is even more important, because pathologic staging is omitted in the case of SABR. The objective of this study was to determine the concordance between clinical and pathologic stage in routine clinical practice for patients with early-stage NSCLC.

### Methods

Prospective data were derived from the Dutch Lung Surgery Audit (DLSA) in 2013 and 2014. Patients with clinical stage I NSCLC who underwent surgical resection and had a positron emission tomography-computed tomography (PET-CT) scan in their clinical workup were selected. Clinical and pathologic TNM (cTNM and pTNM) stages were compared.

### Results

From a total of 1,790 patients with clinical stage I, 1,555 (87%) patients were included in this analysis. Concordance between cTNM and pTNM was 59.9%. Of the patients with clinical stage I, 22.6% were upstaged to pathologic stage II or higher. In total, 14.9% of all patients with clinical stage I had nodal metastases, and 5.5% of all patients had unforeseen N2 disease. In patients with clinical stage T2a tumors, 21.3% had nodal metastases, 14.5% being N1 and 6.7% being N2 disease.

### Conclusions

Concordance between clinical and pathologic stage is 59.9%. In patients with clinical stage I NSCLC, 22.6% were upstaged to pathologic stage II or higher, which is an indication for adjuvant chemotherapy. Improvement in accuracy of staging is thus needed, particularly for these patients.

## INTRODUCTION

Survival of patients with stage I non-small cell lung cancer (NSCLC) remains disappointing, with 5-year survival rates after anatomical surgical resection ranging from 60% to 80%.[1] Staging lung cancer is very difficult, with low accuracy of the staging process.[2-5] The concordance between clinical and pathologic staging in early-stage lung cancer is between 65% and 75%. Most studies on this subject were published in the era before positron emission tomography-computed tomography (PET-CT).[4-7] When understaging a patient with early-stage NSCLC, undertreatment is likely, which might negatively impact survival. In the Netherlands, according to the national evidence-based guideline, the staging algorithm of stage I NSCLC is composed of PET-CT, and in the case of an abnormal PET scan or an enlarged mediastinal node (short-axis diameter >1 cm), invasive diagnostic procedures and histopathologic proof are recommended using endoscopic ultrasound/endobronchial ultrasound (EUS/EBUS). If these examinations prove normal, a mediastinoscopy is indicated. Invasive staging of the mediastinum is also recommended in patients with a central tumor or N1 lymph node involvement. Pathologic proof of the primary tumor is not mandatory preoperatively.[8]

The Dutch Lung Surgery Audit (DLSA) is a nationwide prospective database that is used to monitor the staging process in patients who undergo surgical procedures for early-stage NSCLC. The advantage of such population-based data is that they represent daily practice, rather than selected populations in expert centers.

As clinical staging remains a challenge, so does the treatment of early-stage lung cancer. Surgical intervention and stereotactic ablative radiotherapy (SABR) are effective treatments with different morbidities and potential mortality. Initially SABR was used as a treatment modality for patients unfit for operative treatment.[9,10] Because of excellent results in locoregional control, which have been proved in retrospective and phase II prospective studies, SABR is becoming an alternative treatment used more and more for patients who are also candidates to undergo operative treatment.[11-16]

Recently Chang and colleagues[17] pooled data from 2 prematurely finished randomized trials to conclude that SABR is a good alternative to surgical treatment in patients with stage I NSCLC regarding overall survival, recurrence-free survival at 3 years, local recurrence, regional recurrence, distant metastasis, and complications. Although these are the only randomized controlled data on this subject, the robustness of the

conclusions was strongly challenged. One of the criticisms of the study concerned the lack of final pathologic staging in patients treated with SABR.[18-22] One of the major problems in the absence of surgical staging is the presence of lymph nodes with metastases, with reported rates of 11.7% and almost 5% to 10% being unforeseen pathologic N2 nodes.[7,23] In the case of SABR, such nodes would not receive a therapeutic dose of radiation nor would the patients receive adjuvant chemotherapy.

In an era in which the indication for SABR is being extended with only minimal prospective randomized data available, we aimed to investigate the concordance between clinical (c)TNM and pathologic (p)TNM in early-stage lung cancer, especially with regard to lymph node staging. This article is an in-depth analysis of the stage I cohort from a total study population described elsewhere, given the importance of accurate staging, particularly in patients with stage I disease, because alternative nonsurgical treatment modalities are now available in which there is no definitive pathologic review of the malignancy.

## PATIENTS AND METHODS

### Data source

In the Netherlands, the DLSA started in 2012 as a national prospective clinical database. The objective of this database was to register the care process and the outcome of all patients in routine practice undergoing operative treatment for benign and malignant lung tumors. In 2013 and 2014, 41 of 48 (85%) Dutch hospitals performing operations on patients with lung cancer participated, and 85% of patients undergoing lobectomy because of lung cancer were registered in this database. We used this database to compare cTNM and pTNM in early-stage lung cancer. The clinical stage is defined in the DLSA as the last known stage before resection—after PET-CT, EUS/EBUS, or mediastinoscopy, or a combination of these modalities. Because these data are collected as part of everyday routine clinical practice, no informed consent was mandatory.

### Patients

All patients with clinical stage I NSCLC who underwent an anatomical parenchymal resection (pneumonectomy, lobectomy/bilobectomy, or sublobar resection) between January 1, 2013 and December 31, 2014 and who were registered in the DLSA were evaluated. According to the seventh

edition of TNM: Classification of Malignant Tumours, this is T1a/T1b/T2a disease, meaning a tumor size up to 5 cm, no lymph node invasion, or any size less than 5 cm with invasion of the main stem bronchus but growth greater than 2 cm distal from the carina, or infiltration into the visceral pleura.[24] Disease is also classified as cN0 if nodes/stations are enlarged or show fluorine 18-fluorodeoxyglucose uptake, and those nodes/stations were further evaluated and found to be normal before operation using EUS/EBUS/mediastinoscopy. Minimal data requirements for inclusion in the analysis were information on cTNM and pTNM stages, type of parenchymal resection, and postoperative histopathologic results. Patients who had acute symptoms, a histopathologic type other than NSCLC, neoadjuvant treatment, or no available PET-CT scans were excluded.



**Outcome**

The primary outcome is discrepancy (understaging or overstaging) between cTNM and pTNM stages for the different clinical stages. Secondary outcomes are the patients misdiagnosed based on nodal and tumor stage and the number of patients who should receive adjuvant therapy based on the pathologic outcome. An analysis on accuracy of staging by histologic type was also performed.

The use of invasive diagnostics such as EUS, EBUS, and mediastinoscopy/videomediastinoscopy was carried out in suspicious nodes (enlarged or PET positive) to analyze how close guidelines on staging mediastinal lymph nodes were followed.

**Statistical analysis**

Included patients with clinical stage I disease were compared with excluded patients with clinical stage I disease on a number of preoperative patient and tumor characteristics, using Chi-square tests and Fisher exact tests in case of expected counts less than 5. Patients with clinical stage IA were then compared with patients with clinical stage IB, using Chi-square tests, looking for discrepancy (yes/no) to assess whether discrepancy depended on clinical stage. A univariate analysis for risk factors for inaccurate clinical staging was performed. All statistical analyses were performed in PASW Statistics, version 23 (SPSS, Inc, Chicago, IL).

## RESULTS

### Demographics

From a total of 1,790 patients with clinical stage I NSCLC, 1,555 eligible patients undergoing resection for from January 1, 2013 to December 31, 2014 were included in this analysis. All patients had PET-CT performed preoperatively. Figure 1 shows a flow chart of how patients were included or excluded. Table 1 shows that included patients differed significantly from excluded patients only in that they more often had a lower Eastern Cooperative Oncology Group (ECOG) score and higher diffusion capacity of the lung for carbon monoxide (DLCO) and forced expiratory volume in 1 second ($FEV_1$), suggesting that included patients might be a somewhat healthy selection of the total patient population in the Netherlands.

### Discrepancy between cTNM and pTNM

The total group consisted of 1,555 patients, and 931 patients had a pTNM that matched the cTNM (59.9%) (Table 2). Concordance of the patients with clinical stage IA was higher: 664 patients of a total 1,005 patients had pathologic stage IA disease (66.1%). For stage IB disease, concordance was significantly lower ($p<0.05$), with 267 of the 550 patients having accurate preoperative staging (48.5%). In the patients with clinical stage I disease, 351 (22.6%) patients had pathologic stage IIA or higher, which is an indication for adjuvant chemotherapy in the Netherlands. In a univariate analysis, only male sex (odds ratio [OR], 0.724; 95% confidence interval [CI], 0.562–0.922; $p<0.05$) and clinical stage IB disease significantly increased the likelihood of inaccurate staging (OR, 2.092; 95% CI, 1.627–2.689; $p<0.05$).

### Discrepancy based on clinical tumor and lymph node stages

Table 3 shows an analysis of T stage in which we show how cT stage and pT stage differ. Of the total clinical stage I population, 13 patients had benign or in situ tumor (0.8%). In T1a tumors (<2 cm), 68.9% were accurately staged; in T1b tumors (2–3 cm), 45.2% were accurately staged; and in T2a tumors (3–5 cm), 62.7% were accurately staged based on tumor stage. Table 4 shows an analysis of N stage. In our total cohort of patients with clinical stage I disease, 14.9% had nodal metastases and 5.5% had unforeseen N2 nodes. It is shown that the lower the tumor stage, the fewer nodal metastases and unforeseen N2 nodes are present. In patients with clinical T2a tumor stage, 21.3% has unsuspected pathologic nodal metastases, 14.5% were stage N1 and 6.7% were stage N2. An analysis by histologic type showed

no difference between the different subtypes of NSCLC in the accuracy of staging (p = 0.238).

**Analysis of mediastinal staging**

Table 5 shows an analysis of the mediastinal lymph node stations to ascertain if mediastinal staging was done according to current guidelines. There were 66 lymph node stations that were enlarged or were PET positive, or both. In total, 83 invasive staging procedures were performed (EUS/EBUS/ mediastinoscopy/video- mediastinoscopy) in 57 of these stations. After pathologic review of the specimens after the surgical procedure, 22 lymph node stations proved to be positive for tumor. Because 1 patient may have more than 1 suspicious lymph node station, Table 5 presents data on the number of lymph node stations.



## COMMENT

In this cohort of patients with clinical stage I NSCLC, we found a concordance of 59.9% between cTNM and pTNM. Staging in patients with clinical stage IA NSCLC was better than in patients with stage IB disease (66.1% versus 48.5% concordance). In the whole group of patients with clinical stage I tumors, 14.9% had lymph node metastases and 5.5% had unforeseen pN2 nodes. In our cohort, 351 patients (22.6%) were pathologically upstaged to stage II or higher. Adjuvant treatment is indicated in stage II and higher stages based on results of the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis, which showed survival benefit for patients receiving platinum-based chemotherapy after complete resection of stage II and stage III disease.[25] The data presented in this article underscore the vital importance of accurate staging to identify such patients.

These numbers are concordant with the available literature, although most of the literature dates from the pre-PET-CT era.[3-7,26] In a more recent article published in 2009 by Cerfolio and Bryant,[23] this problem in preoperative staging is addressed as well. In a series of 721 patients with clinical stage I disease, only 405 patients had stage I disease after pathologic evaluation (56%). Of the patients with NSCLC, 32% were understaged clinically. Most understaging resulted from unforeseen pN2 disease (9.6%), even with the use of EUS, EBUS, and mediastinoscopy. In the Cerfolio and Bryant study, patients with pathologic stage IA tumors had a 5-year survival of 80%.

In our series, 22.6% of patients had an indication to receive adjuvant chemotherapy after operative treatment according to Dutch guidelines.[8] This makes surgical resection a very important staging tool in the treatment of stage I lung cancer. The indication for adjuvant therapy would not have become evident without surgical resection, eg, when these patients would have been treated with SABR rather than surgical treatment.

Initially SABR was mainly used to treat patients with a high risk from surgical intervention or patients who were not fit for operation.[27,28] In the study of Senthi and coworkers,[28] a study population was described in which 65% of the patients did not have a histologically confirmed malignancy, making cynics suggest that benign lesions were included. However, when using the same inclusion criteria in patients who underwent resection, other studies from the Netherlands show a percentage of benign lesions of only 4%.[29,30] Unfortunately the DLSA does not register whether histologic proof of the primary tumor was obtained preoperatively: In our study, 0.8% of the patients with clinical stage I proved to have benign lesions. It is not mandatory to obtain histologic proof preoperatively in the Netherlands.

From treating only patients with high surgical risk, the literature regarding SABR has shifted. Two recent retrospective studies from the Netherlands in patients who could also have undergone surgical resection showed excellent results for SABR in early-stage NSCLC, making this a feasible option in surgical patients as well. Long-term results with SABR are excellent in the Netherlands, with low toxicity and locoregional recurrence being lower with SABR than with surgical resection.[12,31] Underlying mechanisms might be immunomodulatory effects, such as T-cell stimulation and tumor necrosis factor-α modulation that may possibly have a favorable effect outside the irradiated area.[32]

Conversely, a recent study by Hamaji and associates[33] pointed out that the nonrandomized literature comparing SABR and surgical treatment particularly should be interpreted with caution: In their series, they found favorable long-term outcomes regarding overall survival, cause-specific survival, recurrence-free survival, local control, and distant control, all in favor of video-assisted thoracoscopy (VATS) lobectomy.[33]

Finally, recently randomized data were published. In a pooled analysis of 2 prospective randomized trials (Radiosurgery Or Surgery for operable Early stage non-small cell Lung cancer [ROSEL] and Randomized Study to Compare CyberKnife to Surgical Resection in Stage I Non-small cell Lung Cancer [STARS] trials), SABR was found to be a good treatment option in early-stage

lung cancer and produced a significantly better overall survival at 3 years.[17] The main criticisms of this study were the lack of definitive pathologic staging when patients were treated with SABR and the methodological weakness of pooling 2 trials with very poor accrual (2.8%), rendering the analysis underpowered.[18-22]

**This study**

We performed an in-depth analysis of the early-stage NSCLC population, from a total population published elsewhere, with this discussion on treatment options in mind. We used the DLSA to compare clinical and pathologic TNM stages in patients who underwent operative treatment for clinical stage I NSCLC. Only 59.9% had pathologic stage I NSCLC. Accuracy by tumor stage varied between 45.2% and 68.9% in this series. It is well documented in the literature that staging tumor size is difficult. CT probably overestimates tumor size compared with pathologic review because of an inflated lung when scanning, as well as inflammation, infiltration, or edema.[34] However, over- or underestimation of tumor size will not change therapeutic decision-making very often. In our study, increasing tumor diameter was associated with increasing hilar lymph node metastasis (pN1 ranging from 6.2%–14.5%). This is the same for unforeseen N2 nodes (4.6%–6.7%). In patients with clinical T2a tumor stage, 21.3% has unsuspected pathologic nodal metastases. With this high number of hilar and mediastinal lymph node metastases, using EUS/EBUS more in this population can be considered, although we showed that these tests have a high number of false-negative results.

We also showed how enlarged or PET-positive (or both) mediastinal lymph node stations were analyzed. There were 66 suspicious lymph node stations, and 57 of these stations were analyzed. It is unclear why 9 stations were not analyzed preoperatively; the DLSA does not provide data on these decisions. Even with the use of EUS/EBUS and mediastinoscopy/videomediastinoscopy, 22 lymph node stations were positive for tumor after surgical sampling or dissection. This is worrisome, because patients undergo invasive diagnostic procedures for staging the mediastinum, but these might provide false-negative results. Our rate of 5.5% unforeseen N2 nodes is in accordance with the current literature, although it might be improved with more accurate use of the invasive diagnostic modalities, which is important because it has therapeutic consequences for patients. An alternative option is a video-

assisted mediastinoscopic lymphadenectomy or VATS nodal dissection preoperatively, although these techniques carry more risk.

**Limitations**

This study has several limitations. First the data is self-reported by doctors or specialized nurses, so bias could be introduced. However, the data are verified by an external organization and compared with the data in the Netherlands Cancer Registry to increase reliability of outcomes. In addition, comparing results of randomized trials with "real life data" has its limitations, although most studies cited in this article come from the same country as the population-based data presented in this article. Unfortunately, the DLSA does not register certain details; therefore we do not have data on histologic proof preoperatively or location of the tumor, e.g., if the tumor was located centrally. Despite these problems, at this point it is the best database representing daily practice in the Netherlands. Comparing patients included with those excluded showed that our data were fairly representative of the total patient population in the Netherlands.

**Implications for clinical practice or future research**

In this series of stage I tumors, we reported a 5.5% rate of unforeseen N2 nodes. This number is similar to that presented in the existing literature. We showed that guidelines in nodal staging are not followed closely and that accuracy of invasive diagnostic modalities is low. Future studies should be directed to the process of medical decision-making and why professionals choose to omit or perform certain diagnostic studies. A protocol is currently written to study the interprofessional variation in diagnostic decision-making more closely.

In this series, 14.9% of patients had lymph node metastases, and 22.6% of patients would be eligible for adjuvant chemotherapy. It is intriguing that studies on SABR in probably quite similar patient groups show excellent results despite possible undertreatment according to the actual pathologic stage. It is crucial to investigate this further in studies with long-term follow-up.

## CONCLUSIONS

This article shows modest accuracy (59.9%) of clinical staging in patients with stage I NSCLC in routine clinical practice. This is mostly because of inaccurate interpretation of the PET-CT scan regarding tumor size and N1 disease. It is also obvious that guidelines for mediastinal staging are not sufficiently adhered to, and accuracy of invasive mediastinal lymph node staging is low. Without the gold standard of pathologic staging after resection, more than 40% of patients with clinical early-stage NSCLC would have been staged inaccurately. As a consequence, based on clinical staging alone, adjuvant chemotherapy would have been denied to 22.6% of our patients.

**TABLE 1.** Baseline characteristics included and excluded patients

| | | Included | | Excluded | | |
|---|---|---|---|---|---|---|
| | | n | % | n | % | p |
| **Sex** | Male (%) | 828 | 53.2 | 135 | 58.2 | 0.17 |
| **Age** | < 75 years | 1,237 | 79.5 | 160 | 69.0 | 0.07 |
| | 75+ years | 309 | 19.9 | 68 | 29.3 | |
| | Missing | 9 | 0.6 | 4 | 1.7 | |
| **ECOG score** | ECOG 0 | 787 | 50.6 | 88 | 37.9 | < 0.05 |
| | ECOG 1 | 394 | 25.3 | 51 | 22.0 | |
| | ECOG 2 | 49 | 3.2 | 5 | 2.2 | |
| | ECOG 3 | 2 | 0.1 | 3 | 1.3 | |
| | ECOG 4 | 1 | 0.1 | 1 | 0.4 | |
| | Missing | 322 | 20.7 | 84 | 36.2 | |
| **DLCO** | >80% | 391 | 25.1 | 45 | 19.4 | < 0.05 |
| | 40-80% | 774 | 49.8 | 113 | 48.7 | |
| | < 40% | 17 | 1.1 | 0 | 0.0 | |
| | missing | 373 | 24.0 | 74 | 31.9 | |
| **FEV1** | >80% | 571 | 36.7 | 69 | 29.7 | < 0.05 |
| | 40-80% | 545 | 35.0 | 78 | 33.6 | |
| | < 40% | 16 | 1.0 | 1 | 0.4 | |
| | missing | 423 | 27.2 | 84 | 36.2 | |
| **Cardiovascular comorbidity** | No | 825 | 53.1 | 105 | 45.3 | 0.96 |
| | Yes | 428 | 27.5 | 54 | 23.3 | |
| | missing | 302 | 19.4 | 73 | 31.5 | |
| **Pulmonary comorbidity** | No | 654 | 42.1 | 79 | 34.1 | 0.42 |
| | Yes | 593 | 38.1 | 82 | 35.3 | |
| | missing | 308 | 19.8 | 71 | 30.6 | |
| **Neurological comorbidity** | No | 992 | 63.8 | 120 | 51.7 | 0.31 |
| | Yes | 210 | 13.5 | 32 | 13.8 | |
| | missing | 353 | 22.7 | 80 | 34.5 | |

**TABLE 1.** Continued

| | | Included | | Excluded | | |
|---|---|---|---|---|---|---|
| | | n | % | n | % | p |
| **Previous thoracic surgery** | No | 1,440 | 92.6 | 205 | 88.4 | 0.64 |
| | Yes | 93 | 6.0 | 20 | 8.6 | |
| | missing | 22 | 1.4 | 7 | 3.0 | |
| **Clinical Stage** | IA | 1,005 | 64.6 | 39 | 16.8 | < 0.05 |
| | IB | 550 | 35.4 | 38 | 16.4 | |
| | Missing | 0 | 0.0 | 155 | 66.8 | |
| **Tumor Stage** | T1a | 549 | 35.3 | 37 | 15.9 | < 0.05 |
| | T1b | 456 | 29.3 | 29 | 12.5 | |
| | T2a | 550 | 35.4 | 67 | 28.9 | |
| | Missing | 0 | 0.0 | 99 | 42.7 | |

DLCO = diffusion capacity of the lung for carbon monoxide
ECOG = Eastern Cooperative Oncology Group
FEV1= forced expiratory volume in 1 second

**TABLE 2.** Crosstable with differences between clinical and pathological stage

| | | Pathological Stage | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Stage 0 | Stage IA | Stage IB | Stage IIA | Stage IIB | Stage IIIA | Stage IIIB | Total | Accurate staging (%) |
| **Clinical Stage** | Stage IA | 10 | 664 | 181 | 67 | 25 | 57 | 1 | 1,005 | 66.1 |
| | Stage IB | 3 | 79 | 267 | 108 | 40 | 53 | 0 | 550 | 48.5 |
| **Total** | | 13 | 743 | 448 | 175 | 65 | 110 | 1 | 1,555 | |

**TABLE 3.** Crosstable with differences between clinical and pathological T-stage

| | | Pathological T-stage | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | pT0 | pTis | pT1a | pT1b | pT2a | pT2b | pT3 | pT4 | Total | Accurate staging (%) |
| **Clinical T-stage** | cT1a | 1 | 4 | 378 | 72 | 76 | 2 | 12 | 4 | 549 | 68.9 |
| | cT1b | 1 | 4 | 84 | 206 | 136 | 6 | 16 | 3 | 456 | 45.2 |
| | cT2a | 1 | 2 | 24 | 66 | 345 | 57 | 47 | 8 | 550 | 62.7 |
| **Total** | | 3 | 10 | 486 | 344 | 557 | 65 | 75 | 15 | 1,555 | |

c = clinical
p = pathologic

**TABLE 4.** Crosstable with differences between clinical and pathological N-stage, stratified for clinical T-stage.

| | | **Pathological stage** | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | pN0 | % | pN1 | % | pN2 | % | Total |
| **Clinical stage** | cT1aN0 | 490 | 89.2 | 34 | 6.2 | 25 | 4.5 | 549 |
| | cT1bN0 | 400 | 87.7 | 32 | 7.0 | 24 | 5.3 | 456 |
| | cT2aN0 | 433 | 78.7 | 80 | 14.5 | 37 | 6.7 | 550 |
| **Total** | cN0 | 1,323 | 85.1 | 146 | 9.4 | 86 | 5.5 | 1,555 |

c = clinical
p = pathologic

**TABLE 5.** Analysis of mediastinal lymph node stations and staging techniques

| Lymph node station | Pre-op lymph node enlarged and/or positive | Invasive diagnostics | EUS | EBUS | (video) mediastinoscopy | Pathology post-op pos |
|---|---|---|---|---|---|---|
| 2L | 1 | 1 | 1 | 1 | 1 | 0 |
| 2R | 5 | 4 | 1 | 4 | 1 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4L | 13 | 12 | 2 | 7 | 10 | 2 |
| 4R | 25 | 20 | 2 | 14 | 13 | 3 |
| 5/6 | 6 | 5 | 1 | 3 | 2 | 5 |
| 7 | 15 | 14 | 2 | 8 | 9 | 11 |
| 8 | 1 | 1 | 1 | 0 | 0 | 1 |
| 9 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 66 | 57 | 10 | 37 | 36 | 22 |

EBUS = endobronchial ultrasound
EUS = endoscopic ultrasound

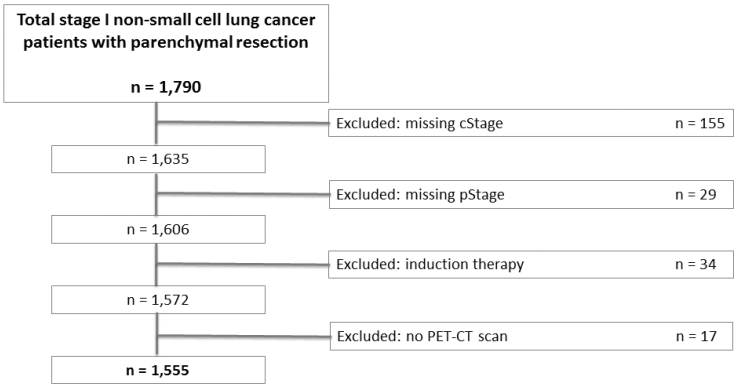


**FIGURE 1.** Flowchart of included and excluded patients

cStage = clinical stage
pStage = pathological stage
PET-CT = positron emission tomography-computed tomography

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# THE DUTCH NATIONAL CLINICAL AUDIT FOR LUNG CANCER: A TOOL TO IMPROVE CLINICAL PRACTICE? AN ANALYSIS OF UNFORESEEN IPSILATERAL MEDIASTINAL LYMPH NODE INVOLVEMENT IN THE DUTCH LUNG SURGERY AUDIT (DLSA).

5

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## ABSTRACT

### Background

Optimal treatment selection for patients with non-small cell lung cancer (NSCLC) depends on the clinical stage of the disease. Particularly patients with mediastinal lymph node involvement (stage IIIA-N2) should be identified since they generally do not benefit from upfront surgery. Although the standardized preoperative use of PET-CT, EUS/EBUS and/or mediastinoscopy identifies most patients with mediastinal lymph node metastasis, a proportion of these patients is only diagnosed after surgery. The objective of this study was to identify all patients with unforeseen N2 disease after surgical resection for NSCLC in a large nationwide database and to evaluate the preoperative clinical staging process.

### Methods

Data was derived from the Dutch Lung Surgery Audit. Patients with pathological stage IIIA NSCLC after an anatomical resection between 2013 and 2015 were evaluated. Clinical and pathological TNM-stage were compared and an analysis was performed on the diagnostic work-up of patients with unforeseen N2 disease.

### Results

From 3,585 patients undergoing surgery for NSCLC between 2013 and 2015, a total of 527 patients with pathological stage IIIA NSCLC were included. Of all 527 patients, 254 patients were upstaged from a clinical N0 (n = 186) or N1 (n = 68) disease to a pathological N2 disease (7.1% unforeseen N2). In these 254 patients, 18 endoscopic ultrasounds, 62 endobronchial ultrasounds and 67 mediastinoscopies were performed preoperatively.

### Conclusions

In real world clinical practice in the Netherlands, the percentage of unforeseen N2 disease in patients undergoing surgery for NSCLC is seven percent. To further reduce this percentage, optimization of the standardized preoperative workup is necessary.

## INTRODUCTION

Accurate clinical staging precedes optimal treatment selection by multidisciplinary tumor boards for patients with non-small cell lung cancer (NSCLC).[1] Clinical overstaging might expose patients to unnecessary toxicity or deprive patients from curative intent treatment, whereas clinical understaging may lead to undertreatment, e.g. omitting induction therapy. Several studies have shown a tendency of lower accuracy of clinical staging for higher stages of NSCLC, mainly attributable to nodal understaging.[2,3] Despite the introduction of routine use of FDG-PET, that resulted in improved clinical staging of NSCLC,[4,5] two recent studies from the Netherlands still report accurate staging in only 51% of patients with upfront surgery for clinical stage IIIA[6] and in 54.6% of patients with clinical stage I-IIIB.[7] In an attempt to improve clinical care for patients with lung cancer in the Netherlands, the Dutch Institute for Clinical Auditing (DICA) introduced the Dutch Lung Surgery Audit (DLSA) in 2011, a prospective national database including clinical data from all patients operated on for lung cancer. Clinical auditing was designed for assessing quality of medical care and to provide benchmarks for treatment outcome.[8-11] The analysis of data from clinical audits provides valuable information on daily clinical practice and outcome, and might potentially identify areas for improvement. In the current study, we evaluate the accuracy of clinical staging for patients with unforeseen mediastinal nodal involvement (N2) using data from the DLSA, and discuss specific issues facilitating improvement of the preoperative staging routine.



## METHODS

After formal approval of the scientific committee of the DLSA, data on patient characteristics, diagnostic work-up, treatment and pathology was derived from the DLSA, a nationwide prospective clinical registry for all patients undergoing surgery for malignant or benign lung and mediastinal disease. Details on the accuracy of the DLSA were previously published. In short, external data verification by independent parties shows good registration quality performed by caregivers and data-managers for most outcome measures (e.g. 30-day mortality, postoperative complications and pathological data).[7] Comparing data of the DLSA with the Netherlands Cancer Registry checks the quality of this database. Queries are sent to individual hospitals to check inconsistencies that are identified and thus ensure a high level of quality of the data.

From the DLSA, all patients with non-small cell lung cancer who had a preoperative PET-CT scan, anatomical parenchymal resection, and pathological stage IIIA (TNM 7th edition[12]) between 2013 and 2015 were identified. Patients who underwent an emergency pulmonary resection, had induction therapy, who were not discussed during multidisciplinary team meeting (MDT), or had an unknown clinical TNM stage prior to surgery, were excluded.

The accuracy of clinical staging was defined as the agreement between clinical and pathological TNM. Clinical stage was defined as the last stage before surgical resection, but after mediastinal staging was completed (e.g. endoscopic ultrasound (EUS), endobronchial ultrasound (EBUS) and/ or mediastinoscopy). The pathological TNM was considered to be the gold standard. A comparison was made between clinical tumor stage (cT) and pathological tumor stage (pT), and between clinical and pathological nodal stage (cN and pN respectively). Unforeseen N2 disease was defined as pathological evidence of tumor in mediastinal lymph nodes in patients with clinical nodal stage N0 or N1. Patients with unforeseen N2 were identified and selected for evaluation of the use of preoperative invasive mediastinal procedures (EUS/EBUS/ mediastinoscopy). Lymph nodes showing FDG uptake on a preoperative PET-scan, or their short axis measuring >1 cm on CT-scan, were marked as clinically tumor positive.

Descriptive statistics were used for all analyses. In case of categorical variables the percentage of each group is shown, where numeric variables are expressed by the mean or median.

## RESULTS

Between January 2013 and December 2015, 3,585 patients from 41 hospitals who had a preoperative PET-CT scan followed by anatomical surgical resection, were registered in the DLSA. From this group, 619 patients had pathological stage IIIA primary NSCLC. Excluded were patients who required an emergency resection (n = 15), patients who received induction therapy (chemotherapy n = 21, chemoradiotherapy n = 26, biologicals n = 1), patients who were not discussed in a MDT (n = 5), and patients without registered clinical TNM (n = 24), leaving 527 patients eligible for this analysis (Figure 1). Patient characteristics are presented in Table 1.

After operation, pathological examination revealed agreement between cTNM and pTNM in 27.5% (145 of 527) of patients with pathological IIIA. A

lower clinical stage was found in 70.6% (n = 372) of patients. When analyzing clinical T- and N descriptors separately, the T-descriptor was accurately staged in 57.1% (301/527) (Table 2) and nodal staging was correct in 28.5% (150/527) of patients (Table 3). For pN0, pN1 and pN2 this was 83.3% (45/54), 36.5% (65/ 178) and 13.6% (40/295), respectively. In total, 254 patients with clinical N0-1 were upstaged to pathological (unforeseen) N2, resulting in 7.1% (254/3,585) unforeseen N2 nodes.

For the total group of 254 patients with unforeseen N2, 114 patients (44.9%) underwent at least one invasive mediastinal diagnostic study (18 EUS, 62 EBUS and 67 mediastinoscopies). In those patients with suspicion of mediastinal nodal involvement on preoperative PET-CT (n = 46, 18.1%), 38 patients were analyzed with 38 EUS, 8 EBUS and 28 mediastinoscopies. However, all these interventions proved false negative since final pathological examination after surgery showed N2 disease of the mediastinum (Table 4). When comparing open surgery to VATS surgery no difference in upstaging to unforeseen N2 was found (data not shown).



## DISCUSSION

In this study of 527 patients with pathological stage IIIA disease, the majority of patients had a discordant, lower clinical TNM (372/527 patients, 70.6%). Unforeseen mediastinal lymph node involvement was greatly responsible for this finding. The percentage of patients diagnosed with unforeseen N2 disease in the Netherlands (7.1%) is comparable to other series.[13,14] Patients with unforeseen mediastinal lymph node involvement are not treated according to current guidelines, which recommend radical chemoradiotherapy or induction therapy followed by surgery as curative intent treatment options for patients with mediastinal lymph node involvement. This might have negative impact on survival.[15-18]

In patients with pathological stage IIIA, the pathological T-descriptor was in 57.1% in agreement with the clinical T-descriptor. Clinical overestimation of tumor size is a well-known phenomenon, explained by an inflated lung during CT-scan investigation, inflammation of the affected area or edema.[17] A higher T stage on pathological examination when compared with the clinical T-stage might be explained by a more central localization of the tumor, tumor infiltration of the pleura or an unexpected extra tumor nodule in the lobe, or by an increase in tumor volume during the time between clinical staging and surgical resection. Unfortunately, these parameters are not



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registered in the current edition of the DLSA. Recently, several proposals for documenting the T-descriptor in more detail have been made by the scientific board of the DLSA. These changes will be implemented in future editions of the dataset.

Of all 254 patients with unforeseen N2-disease, only a few patients (n = 46) had lymph nodes that were positive on FDG-PET scan or enlarged on CT-scan (meaning short axis diameter > 1 cm) and in a majority of these patients (n = 38), invasive diagnostics were used. Unfortunately, it is not recorded why 8 patients did not undergo invasive mediastinal staging procedures. Although 114 patients with unforeseen mediastinal nodal involvement had no suspected mediastinal nodes on FDG-PET, 147 invasive diagnostic procedures were performed in these patients in an attempt to prove mediastinal lymph node involvement. In accordance with recent European and Dutch guidelines for mediastinal staging, we assume that this was done for patients with clinical N1 nodes (in this series 140 patients in total), central tumors, or tumors exceeding 3 cm.[18,19] However, except for clinical N1 involvement, these parameters are not recorded in the current edition of the DLSA dataset. Interesting is why all these invasive investigations were false negative. Possible explanations are sampling error, unsuccessful fine needle aspiration, micrometastasis or the absence of PET-positive or enlarged nodes to aim for during minimally invasive mediastinal staging procedures. Dooms et al.[20] investigated the performance of endosonographic staging in 100 patients with cN1 disease and found that the sensitivity for the detection of N2 disease was only 38%. With the addition of a mediastinoscopy, the sensitivity increased to 73%. Probably it is in these patients that, with relative low pre-test likelihood and expected low tumor volume (PET-CT negative for N2), more invasive techniques such as mediastinoscopy should be considered more liberally.[21] The results of the ASTER 3 trial will address this issue.[22] Furthermore, accuracy of invasive techniques is highly dependent on the operator and hospital protocol, which are variables not registered in the DLSA.[23] Another issue rising from the literature is the suggestion that level 5 or 6 lymph nodes might be considered as N1 nodes in patients with left upper lobe tumors, since their prognosis equals patients with hilar lymph node metastasis in tumors arising in different lobes. In this series of 254 unforeseen N2 patients, there were 52 patients that had positive lymph nodes in level 5 or 6 after resection of a left upper lobe (lobectomy or segmentectomy). It is unclear whether these patients would benefit from induction therapy.[24]

Another interesting finding was that 40 patients with clinical N2 disease were operated upfront, without receiving induction therapy. This treatment strategy is not supported by current guidelines.[15]

The reason why participants of MDT's did not follow guidelines regarding invasive mediastinal staging or omitted induction therapy deliberately, is unclear from the data available from the DLSA.

The data in the DLSA registration is recorded by physicians, nurses and data managers, a fact that might potentially bias recorded information. However, the entered data is randomly checked by an external organization, concluding good registration quality of most important outcome measures (e.g. 30-day mortality, postoperative complications and pathological TNM). Therefore, it is the best available evidence on current daily practice in the Netherlands. However, the database was predominantly designed for the evaluation of surgical quality of care and clinical auditing. To reduce the registration burden, detailed information is often limited in these databases. As a result, several aspects of the diagnostic process or the non-surgical treatment (e.g. induction therapy) are only partially recorded in the registration. This fact might hamper its usefulness in the formation of robust conclusions and recommendations for the improvement of clinical care, and in this specific study, clinical staging, which is illustrated by the following examples. First, regarding the clinical T-descriptor, no information is registered on the exact location of the tumor (central versus peripheral), neither there is for the exact tumor diameter in millimeters or pleural involvement. Therefore, whether the mediastinum was correctly staged by invasive techniques in patients with central tumor location, or whether a tumor is classified as T3 because of its tumor diameter (>7 cm) or because of the appearance of separate nodes in the same lobe, could not be analyzed with the available data. What adds to this discussion, is the lack of a reliable definition for central tumors. This issue has been recognized by the scientific committee of the DLSA, and will be addressed in updates of the registration system, so future analyses might more reliably reflect guideline adherence in patients with specific tumor characteristics. A second example is that there is no distinction between micro- and macro-metastasis, which is considered to be an important difference pathologically and subsequently for prognosis.[25]

Third, for the purpose of this study, we chose pTNM as the gold standard. However, the accuracy of the pTNM is highly dependent on the accuracy of the lymph node dissection during the surgical procedure.[7] Unfortunately,

the accuracy of the lymph node dissection is not registered in the dataset, since participants only register what lymph node stations were biopsied, but not how many nodes were harvested and whether sampling or dissection was used.
Some of these issues have been recognized by the scientific committee of the DLSA, and will be addressed in updates of the registration system, so future analyses might more reliably reflect whether there is guideline adherence in patients with specific tumor characteristics. Despite these limitations, data from the DLSA is quickly accessible facilitating the availability of feedback to health care providers and thus stimulating improvement on several aspects of clinical care. This is comparable to how the Dutch Colorectal Audit is used.[9]
Although we recognize important limitations of the dataset, currently this is the best available instrument to gain insight in current daily clinical practice for patients with stage IIIA in the Netherlands. The optimal number of variables in the database in order to audit and perform scientific research at a high level is a delicate balance between the amount of variables needed to make solid conclusions and recommendations and, on the other hand, the workload for the participating clinicians. Other studies have shown that the DLSA is very suitable for outcome research, and gives direction for new prospective research projects.[7] From 2017, pulmonologists and radiotherapists joined surgeons to participate in a multidisciplinary clinical audit for lung cancer (Dutch Lung Cancer Audit). With this more detailed dataset, together with the additional information of pulmonary oncologists and radiotherapists, interventions on a national level, such as protocolled performance of individual staging procedures and improved guidelines adherence, might improve the standard of care for lung cancer patients.

In conclusion, the DLSA is a valuable instrument for auditing clinical practice and providing feedback to clinicians. Although it was designed for clinical auditing, the dataset is also used for scientific purposes. Nevertheless, the number of variables and completeness of data make conclusions to be interpreted with caution. Continuous improvements in the dataset, extending it with multidisciplinary participants, e.g. radiotherapists and pulmonary oncologists, and thorough analysis of the data, reveals areas for improvement, such as clinical staging in NSCLC.

**TABLE 1.** Basic characteristic of patients with pathological stage IIIA NSCLC undergoing surgical resection between 2013-2015.

| **Pathologic stage IIIA NSCLC** | | **N=527** | |
|---|---|---|---|
| | | N | % |
| **Age, years (mean, median)** | | 67 [68] | |
| **Age, years** | < 60 | 106 | 20.1 |
| | 60-69 | 202 | 38.3 |
| | 70-79 | 187 | 35.5 |
| | ≥ 80 | 32 | 6.1 |
| **Sex** | male | 308 | 58.4 |
| | female | 219 | 41.6 |
| **ASA score**[a] | I-II | 381 | 72.3 |
| | ≥ III | 132 | 25.0 |
| | unknown | 14 | 2.7 |
| **Charlson score**[b] | 0 | 190 | 36.1 |
| | 1 | 147 | 27.9 |
| | 2+ | 190 | 36.1 |
| **DLCO%**[c] | < 40% | 12 | 2.3 |
| | 40-80% | 273 | 51.8 |
| | > 80% | 138 | 26.2 |
| | unknown | 104 | 19.7 |
| **FEV1%**[d] | < 40% | 5 | 0.9 |
| | 40-80% | 176 | 33.4 |
| | > 80% | 206 | 39.1 |
| | unknown | 140 | 26.6 |

[a] American Society of Anaesthesiologists score
[b] Charlson Comorbidity Index
[c] DLCO = diffuse capacity of the lung for carbon monoxide
[d] FEV1 = forced expiratory volume in 1 second

**TABLE 2.** Comparison of clinical and pathological T stage (cT and pT) in patients with a pathological (pTNM) stage IIIA NSCLC.

| | | pT stage | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | T1 N=69 | | T2 N=155 | | T3 N=217 | | T4 N=86 | | Total N=527 |
| | | N | % | N | % | N | % | N | % | N |
| **cT stage** | T1 | 58 | 84.1 | 40 | 25.8 | 17 | 7.8 | 9 | 10.5 | 124 |
| | T2 | 7 | 10.1 | 94 | 60.6 | 70 | 32.3 | 23 | 26.7 | 194 |
| | T3 | 4 | 5.8 | 17 | 11.0 | 119 | 54.8 | 24 | 27.9 | 164 |
| | T4 | 0 | 0.0 | 4 | 2.6 | 11 | 5.1 | 30 | 34.9 | 45 |

**TABLE 3.** Comparison of clinical and pathological N stage (cN and pN) in patients with a pathological (pTNM) stage IIIA NSCLC.

| | | pN stage | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | N0 N=54 | | N1 N=178 | | N2 N=295 | | Total N=527 |
| | | N | % | N | % | N | % | N |
| **cN stage** | N0 | 45 | 83.3 | 100 | 56.2 | 186 | 63.1 | 331 |
| | N1 | 7 | 13.0 | 65 | 36.5 | 68 | 23.1 | 140 |
| | N2 | 1 | 1.9 | 12 | 6.7 | 40 | 13.6 | 53 |
| | N3 | 1 | 1.9 | 1 | 0.6 | 1 | 0.3 | 3 |

**TABLE 4.** Clinical work-up, including invasive diagnostics, in patients with pathologic stage IIIA NSCLC and unforeseen N2 (N=254)
*Patients are divided by clinical stage. For each stage, information is shown on the number of patients with suspected N2 nodes on diagnostic PET-CT and how many patients had any form of invasive mediastinal evaluation in the diagnostic work-up (invasive mediastinal evaluation), EUS, EBUS or mediastinoscopy.*

| | | | N2 suspected on PET-CT/CT-scan | Invasive mediastinal evaluation | EUS | EBUS | Mediastinoscopy |
|---|---|---|---|---|---|---|---|
| | | | N (%) | N | N | N | N |
| Clinical stage* | Stage I | *(N=130)* | 13 (10%) | 33 | 5 | 20 | 20 |
| | Stage II | *(N=103)* | 25 (24%) | 63 | 10 | 35 | 37 |
| | Stage IIIA | *(N=19)* | 8 (42%) | 16 | 2 | 7 | 9 |
| | Stage IIIB / IV | *(N=2)* | 0 (0%) | 2 | 1 | 0 | 1 |

EUS = Endoscopic UltraSound
EBUS = EndoBronchial UltraSound
* Tumor Node Metastasis system (7th edition)

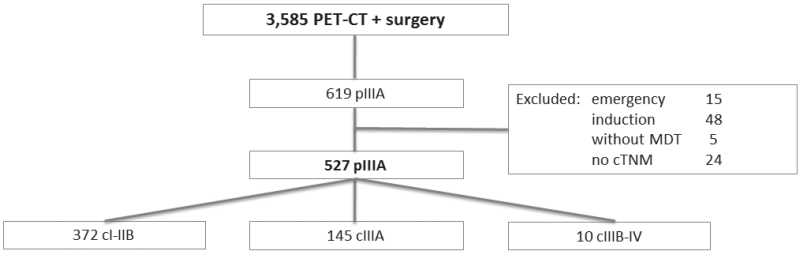


**FIGURE 1.** Flowchart of selection of patients with stage IIIA-N2 disease.

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# MEDIASTINOSCOPY FOR STAGING OF NON-SMALL CELL LUNG CANCER: SURGICAL PERFORMANCE IN THE NETHERLANDS

6

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## ABSTRACT

### Background

Accurate staging of the mediastinal lymph nodes is of great importance to determine optimal treatment options in non-small cell lung cancer (NSCLC). In case of suspected mediastinal metastases, endoscopic/endobronchial ultrasound combined with mediastinoscopy is the gold standard. The diagnostic value of these procedures stands or falls by how they are technically performed. This study used data from the Dutch Lung Cancer Audit for Surgery to evaluate surgical performance of mediastinoscopies in The Netherlands.

### Methods

The study included all patients with a mediastinoscopy for staging of NSCLC and subsequent resection from 2012 to 2016. Complete case analysis was performed, excluding patients with missing data on biopsies or tumor side. Location and number of biopsied stations and adherence to guidelines for performing mediastinoscopy were analyzed. The proportion of unforeseen mediastinal lymph node metastases (unforeseen N2) was compared between mediastinoscopies that did or did not comply with the Dutch guideline.

### Results

The analysis included 1,729 patients. Mediastinoscopies were performed according to the Dutch guideline (requirements: biopsies of 2 ipsilateral stations, 1 contralateral station, and N7) in 51.4% (n = 888) and according to the European Society of Thoracic Surgeons guideline (N4 left, N4 right, and N7) in 75.4% (n = 1,303). Overall, unforeseen N2 was present in 10.2% (n = 140). In mediastinoscopies performed according to the Dutch guideline, unforeseen N2 occurred less often (8.6%) than in the nonadherence group (11.9%; p = 0.043).

### Conclusions

There is improvement potential in surgical performance of mediastinoscopy in the Netherlands, which is reflected by the percentage of guideline adherence and the occurrence of unforeseen N2.

## INTRODUCTION

Clinical mediastinal lymph node staging in patients with non-small cell lung cancer (NSCLC) is challenging. This is reflected by 6.3% unforeseen mediastinal lymph node metastases (unforeseen N2) in all patients undergoing upfront surgical intervention for NSCLC in the Netherlands.[1] For both prognosis and selection of the best treatment, however, adequate mediastinal staging is critical. In the presence of mediastinal metastases, upfront surgical intervention has not demonstrated survival benefits, and according to recent studies and guidelines, definitive chemoradiotherapy or induction therapy, followed by surgical intervention, should be the first treatments of choice.[2-5]

Guidelines recommend invasive mediastinal staging in patients with suspicious (mediastinal) lymph nodes on computed tomography or fluorodeoxyglucose positron emission tomography (FDG-PET). Tumors larger than 3 cm and central tumors are criteria to perform invasive mediastinal staging as well. The Dutch guideline also advises mediastinal staging in tumors that are not FDG avid. When endoscopic ultrasound (EUS) or endobronchial ultrasound (EBUS), or both, with fine needle aspiration do not provide pathologic evidence of lymph node metastases, performing a cervical (video-assisted) mediastinoscopy (hereafter referred to as "mediastinoscopy") is recommended.[6-9]

The role of mediastinoscopy in the staging process is changing. The introduction of FDG-PET allows more specific lymph node sampling and with the increased use of EUS/EBUS - with high sensitivity and specificity and benefits regarding safety and comfort for the patients - the added value of mediastinoscopy has become a topic of debate. Annema and colleagues showed that even when EUS/EBUS are performed by a skilled endoscopist, by additional mediastinoscopy the sensitivity of detection of mediastinal nodal disease rises to 94%. Sensitivity for EUS/EBUS alone is 85%.[9] However, whether all patients with a negative EUS/EBUS require a mediastinoscopy is still unclear. Efforts are made to identify homogeneous subgroups that will likely benefit from additional mediastinoscopy.[10-12] In daily practice, the use of mediastinoscopy already seems to be progressively reserved for patients with high suspicion of N2 disease instead of being regularly used after negative EUS/EBUS.[13]

The quality of mediastinoscopy has always been a subject of discussion because it is related to the extent of lymph node sampling and surgeons' experience.[11,14,15] Therefore, when comparing staging strategies with or





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without mediastinoscopy, the quality and extent of biopsies are highly relevant and should be taken into account. This study evaluated the surgical performance of mediastinoscopy for mediastinal staging in daily clinical practice in The Netherlands, by assessing guideline adherence and unforeseen N2 disease, using data from the Dutch Lung Cancer Audit for Surgery (DLCA-S).[16]

## PATIENTS AND METHODS

### Patient selection

Data were retrieved from the DLCA-S, a prospective, national quality registry introduced in 2012, covering all surgical procedures in The Netherlands for malignant or benign lung and mediastinal disease.[16]

All registered patients with a mediastinal operation for staging of NSCLC between January 1, 2012, and December 31, 2016, were identified. Patients with cervical mediastinoscopy and subsequent resection were included when a FDG-PET was performed and a minimum set of variables was registered: sex, date of birth, date of operation, type of operation, and vital status 30 days after the operation or at the time of discharge. Patients with missing data on biopsies or pathology and patients with an unknown tumor side were excluded. For the analysis on unforeseen N2 disease, patients with positive mediastinoscopy, treated with induction therapy or clinically staged as cN2 were excluded (n = 353), this last group to avoid bias. These patients likely had a high suspicion of N2 disease but were nevertheless operated on because invasive staging failed to prove so.

### Definitions and guideline criteria

The DLCA-S does not make a distinction between “biopsies”, “dissection”, or “sampling”; therefore, the term “biopsied” is used in this study for all of these options.

According to the Dutch guideline on the diagnosis and treatment of NSCLC, an adequate mediastinoscopy requires biopsy samples from at least 4 of 6 “accessible” lymph node stations: 2 ipsilateral, 1 contralateral, and station 7. Stations classified as accessible in this guideline are stations 1, 2R, 2L, 4R, 4L, and 7.[6] The European Society of Thoracic Surgeons (ESTS) guideline recommends taking biopsy samples of at least station 4L, 4R, and 7. In addition, station 2L and 2R can be biopsied.[8]

In The Netherlands, lung surgery is performed only by specialized surgeons who have followed a training program and have to comply with quality and quantity standards.

**Outcomes**

The primary outcomes assessed were overall guideline adherence according to the Dutch guideline and the proportion of postoperative unforeseen N2 disease. To assess whether guideline adherence leads to a better outcome, the proportion of unforeseen N2 disease was compared for groups based on guideline adherence. Secondary outcomes were ESTS guideline adherence, between-hospital variation in guideline adherence, the proportion of true false negatives, and comparison of major complications (wound infection/ mediastinitis, recurrent laryngeal nerve injury, tracheal injury, complications requiring reintervention, or death) between groups based on guideline adherence.

**Statistical analysis**

The influence of patient and tumor characteristics on guideline adherence was analyzed by a univariable comparison of patients with a mediastinoscopy performed according to the Dutch guideline or not, using Chi-square tests. Between-hospital variation in guideline adherence was presented in funnel plots with 95% confidence intervals. Proportions of unforeseen N2 and true false negatives were calculated and compared for groups based on adherence to both the Dutch and ESTS guideline by Chi-square test. Major complications between patients with and without guideline adherence were compared by Chi-square test. For patients with unforeseen N2, the use and results of (invasive) diagnostics were investigated—stratified by nodal station—to analyze the adherence to guidelines on mediastinal lymph node staging. SPSS 25.0 software (IBM, Armonk, NY) was used for statistical analysis, and p values of less than 0.05 were considered statistically significant.

## RESULTS

### Patients

Between January 1, 2012, and December 31, 2016, 1,882 eligible patients were registered. After exclusion of patients with missing data, 1,729 patients were included (Figure 1).

### Biopsied lymph node stations

The median number of lymph node stations biopsied per mediastinoscopy was 4 (Figure 2A). In 65.9% (n = 1,140) of the patients, 4 or more stations were biopsied, which is the least needed to meet the Dutch guideline criteria. Figure 2B demonstrates the percentage of mediastinoscopies in which a particular station was biopsied per lymph node station, stratified for tumor side. Overall, right-sided lymph node stations were relatively more frequently biopsied than left sided stations, regardless of the tumor side.

### Guideline adherence and between-hospital variation

When the performed mediastinoscopies were compared with the Dutch guideline, the required lymph node stations corresponding with the primary tumor location were biopsied in 51.4% (n = 888). There were no significant differences in baseline patient and tumor characteristics when comparing patients with and without a mediastinoscopy performed in accordance with the Dutch guideline (Table 1), except for tumor location.

Compared with the ESTS guideline, adherence was 75.4% (n = 1,303). As reported in Table 2, in lobe-specific guideline adherence there is more variation seen for the Dutch guideline (range, 41.3% to 72.7% vs 68.8% to 87.9%).

Considerable between-hospital variation is seen on guideline adherence for the two guidelines (Figure 3). Compared with the Dutch guideline (Figure 3A), 4 hospitals performed significantly better than the national average, and 10 hospitals performed significantly worse. Among these underperforming hospitals, 4 low-volume hospitals were still underperforming compared with the ESTS guideline (Figure 3B).

### Unforeseen N2 disease

Postoperative histopathology showed unforeseen N2 disease in 140 of 1,376 patients (10.2%). In patients with a mediastinoscopy performed according to the Dutch guideline, the unforeseen N2 rate was 8.6% (n = 60). After a mediastinoscopy without Dutch guideline adherence, the unforeseen N2

rate was 11.9% (n = 80; p = 0.043). For major complications, no significant difference was found between the groups (adherence, 2.5%; no adherence, 1.5%; p = 0.169). When both groups were compared following the ESTS guideline, no difference in unforeseen N2 could be demonstrated: 10.1% (n = 106) versus 10.3% (n = 34; p = 0.912).

In the 140 patients with unforeseen N2 disease, the primary tumor was located in the left lung in 78 patients (55.7%) and in the right in 62 patients (44.3%). In 61 patients, unforeseen N2 disease occurred in mediastinal lymph node stations unreachable by cervical mediastinoscopy (station 5, 6, 8, or 9). This corresponds with a true false-negative rate of 5.7% (no clinically relevant or significant difference between adherence and non-adherence groups for the Dutch and ESTS guidelines). Table 3 reports an in-depth analysis on lymph node station level of all of the 140 mediastinoscopies revealing postoperative unforeseen N2. Of the 76 accessible lymph node stations (ie, 2L/R, 4L/R, and 7; highlighted in Table 3) with postoperative unforeseen N2 disease, 65 were biopsied during mediastinoscopy. Only in 21 of 76 cases was the specific lymph node enlarged or positive on computed tomography/FDG-PET.



## COMMENT

In The Netherlands, adherence to the Dutch guideline for performing mediastinoscopy in patients with NSCLC is 51%, with considerable between-hospital variation. Unforeseen N2 disease is present in 10.2% of patients subsequently undergoing resection and was significantly less in patients with a mediastinoscopy performed according to the Dutch guideline. These results suggest room for improvement.

Mediastinoscopy is a technically challenging procedure. Quality of the procedure (extent of sampling and surgeons' experience) influences the quality of staging. Existing studies on surgical performance of mediastinoscopy are mostly of a retrospective nature and are based on data from single centers where sufficient procedures have been performed and where administration and follow-up have been adequate.[14,17-20] The DLCA-S allows analysis on a national level, reflecting daily practice in a period where experience levels might have decreased as a result of the introduction of EBUS/EUS.

In this national database study, mediastinoscopy was performed according to the Dutch guideline in 51% of 1,729 included patients. When the less

strict ESTS guideline is taken as a reference, 75% of mediastinoscopies were performed accordingly. Previous comparisons with the ESTS guideline by Smulders and colleagues and Steunenberg and colleagues showed adherence of 40% (1993 to 1999) and 50% (2009 to 2014), respectively.[14,18] This study is the first study analyzing (nationwide) adherence to the Dutch guideline.

In the distribution of the number of biopsied stations (median, 4), an increase is seen compared with Steunenberg and colleagues[14] (median, 3; 2009 to 2014) and van Albada and colleagues[19] (median, 1; 1994 to 2000). Results are similar to those of Verhagen and colleagues[13] (median, 4; 2009 to 2012). Hypotheses for the differences between these previous studies and the current study are: First, introduction of innovations such as FDG-PET, EUS/EBUS - which help direct biopsies and enable better indications for invasive staging - and videomediastinoscopy will have contributed.[21]

Second, results of previous studies probably have raised awareness on the quality of the surgical performance of mediastinoscopy, and (surgical) quality is a topic that has gained more attention in general, with focus on quality registries and outcome research.

Third, prospective and mandatory registration of surgical characteristics of all performed mediastinoscopies will have improved reporting and documentation and will have raised focus on performance and guideline adherence, potentially resulting in improved outcomes.[22]

The ESTS guideline is less strict in its recommendations: sampling of a second ipsilateral nodal station is not required. Other explanations for the low compliance with the Dutch guideline could be (1) the difficulty of finding level 2 - especially the upper tracheal lymph node stations (2L and 2R) were biopsied less frequently; and (2) difficulty in anatomical differentiation between level 2 and level 4 in a mediastinoscopy. That adherence for left-sided tumors was lower supports these arguments, because station 2L is known to be hard to reach (Table 2). Also, surgeons could have chosen to follow the ESTS instead of the national guideline. The funnel plots (Figure 3) show wider interhospital variation on surgical performance and more underperforming hospitals - hospitals below the 95% confidence interval - for the Dutch guideline, which supports this last hypothesis. The considerable between-hospital variation offers room for improvement.

The 10.2% unforeseen N2 disease in patients who underwent resection after mediastinoscopy in this study is in line with the ESTS guideline, which states that a rate of unforeseen N2 disease of 10% is acceptable.[8] Other

studies show unforeseen N2 rates of 5.5%,[17] 8.2%,[23] 10.0%,[13] and 17.0%.[18] The study by Smulders and colleagues[18] (17.0%) is the oldest and was performed in an era before FDG-PET and video mediastinoscopy. This, and lower guideline adherence than in the current study, have probably led to a higher unforeseen N2 rate. Lemaire and colleagues[17] (unforeseen N2 rate, 5.5%; 1996 to 2005) performed their evaluation of conventional mediastinoscopy in a single center that performed more than 200 mediastinoscopies yearly. Experience (reflected by high case volume) might play a role in their low unforeseen N2 rates. However, it is important to keep in mind that the finding of false negative results is also affected by the quality of the lymph node dissection during resection, which could account for underestimations of the unforeseen N2 rate. Therefore, drawing solid conclusions from the comparison of these results remains difficult.

For the Dutch guideline, a significant difference is seen in unforeseen N2 disease comparing patients staged (8.6%) and not staged (11.9%) according to the guideline ($p = 0.043$). More extensive sampling and therefore better detection might be the explanation for this effect, but adequate performance of mediastinoscopy could also be an expression of a well-organized staging process and play a role here. Also, more left-sided tumors were pre- sent in the nonadherence group. Inaccessibility of station 5 and 6 by cervical mediastinoscopy will partly explain this. The difference in unforeseen N2 disease is not present when comparing groups according to the ESTS guideline or when comparing the "true" false-negative rates where only nodal stations accessible by mediastinoscopy are taken into account.

A possible explanation might be a more extensive mediastinal lymph node sampling when following the Dutch guideline that results in finding more (micro)metastases. Because patients with (minimal) N2 disease are eligible for neoadjuvant treatment, this is important with regard to the optimal treatment strategy. Detection of N2 disease in station 5 and 6 can be improved, for example, by performing an anterior parasternal mediastinotomy (Chamberlain procedure).[24] However, how necessary this is questionable because metastases in these stations are more and more seen as a "sentinel node" for left upper-lobe tumors and, therefore, no contraindication for resection and not of influence for treatment choices alone.

In-depth analysis of the "false negative" cases (Table 3) shows that most of the postoperative positive nodal stations—that were accessible in mediastinoscopy—were actually biopsied during mediastinoscopy (eg,

16 of 18 for 4R). Only in a few patients were these stations suspected on computed tomography/PET (6 of 18 for 4R). This suggests that most of the unforeseen N2 cases were based on micrometastases in stations accessible with mediastinoscopy or were present in stations not accessible with mediastinoscopy. Other studies show similar results.[17,25] Also, station 7 was tumor positive in 41 of the 47 cases, despite biopsies by mediastinoscopy. This might be because of metastases located in the lower aspect of the subcarinal region, which is known to be hard to assess during mediastinoscopy.[26] The use of EUS might be more contributory in these cases but was only performed in 57% of these patients.

This study has some limitations. Data in the DLCA-S are primarily collected for evaluation of surgical quality of care. To reduce the registration burden, collected information is often limited and not always as detailed as desired for research purposes. For example, conventional mediastinoscopy and video-assisted mediastinoscopy are clustered in one group, which makes distinction impossible. However, almost all Dutch hospitals now use video-assisted mediastinoscopy, with only few exceptions.[21] Also, only for patients undergoing surgical resection of NSCLC is detailed information collected on patient and tumor characteristics. For a substantial group of NSCLC patients with a positive mediastinoscopy or with negative mediastinoscopy but no pulmonary resection (n = 1,110), insufficient data were available to include them. Especially data on tumor side (necessary to evaluate guideline adherence) and on histopathology (inclusion of NSCLC only) were essential. By not including these patients, selection bias might have been introduced. However, the distribution of the number of biopsied stations and adherence to the ESTS guideline in this group were not different compared with included patients.

Next, information on the number of biopsied single lymph nodes and the weight of the total lymph nodes procured could have given more insights about adequate performance, but both were not registered in the DLCA-S. Finally, data are self-reported by hospitals, by data managers, doctors, and specialized nurses. This could have introduced bias. External verification of DLCA-S data showed high levels of patient inclusion and good quality of the registered data on mortality and complications.[27] Although performance and outcomes of mediastinoscopy were not among the verified items, this verification suggest adequate and reliable data collection.



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In conclusion, this study of national data of 1,729 patients shows that there is still room for improvement of surgical performance of mediastinoscopy. This is reflected by the percentage of guideline adherence, between-hospital variation in guideline adherence, and the occurrence of unforeseen N2. In mediastinoscopies performed according to the Dutch guidelines, less unforeseen N2 disease was found. Awareness of the extent of lymph node biopsies is therefore important, and performance of mediastinoscopy according to guidelines will therefore be added as a quality indicator for the Dutch national audit. In the discussion on added value of mediastinoscopy it is important to consider surgical quality of the procedure and to realize that accuracy of staging procedures is subject to how a procedure is technically performed.

**TABLE 1.** Distribution of patient and tumor characteristics of all patients and patients staged and not staged according to the Dutch guideline.

| **Patient characteristics** | | All N=1,729 | | Guideline + n=888 (51.4%) | | Guideline - n=841 (48.6%) | | |
|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | p |
| **Age (mean [SD])** | | 66.9 [8.9] | | 67.2 [8.9] | | 66.6 [8.9] | | |
| **Sex** | Male | 1,133 | 65.5 | 577 | 65.0 | 556 | 66.1 | 0.620 |
| | Female | 596 | 34.5 | 311 | 35.0 | 285 | 33.9 | |
| **ECOG score** | 0-I | 1,406 | 81.3 | 730 | 82.2 | 676 | 80.4 | 0.308 |
| | II+ | 81 | 4.7 | 35 | 3.9 | 46 | 5.5 | |
| | Unknown/missing | 242 | 14.0 | 123 | 13.9 | 119 | 14.1 | |
| **DLCO˜** | >80% | 391 | 22.6 | 188 | 21.2 | 203 | 24.1 | 0.263 |
| | 40-80% | 960 | 55.5 | 494 | 55.6 | 466 | 55.4 | |
| | <40% | 32 | 1.9 | 15 | 1.7 | 17 | 2.0 | |
| | Unknown/missing | 346 | 20.0 | 191 | 21.5 | 155 | 18.4 | |
| **FEV1ˆ** | >80% | 630 | 36.4 | 327 | 36.8 | 303 | 36.0 | 0.168 |
| | 40-80% | 673 | 38.9 | 334 | 37.6 | 339 | 40.3 | |
| | <40% | 14 | 0.8 | 4 | 0.5 | 10 | 1.2 | |
| | Unknown/missing | 412 | 23.8 | 233 | 25.1 | 189 | 22.5 | |
| **ASA score**** | I-II | 1,198 | 69.3 | 602 | 67.8 | 596 | 70.9 | 0.306 |
| | III+ | 492 | 28.5 | 267 | 30.1 | 225 | 26.8 | |
| | Unknown/missing | 39 | 2.3 | 19 | 2.1 | 20 | 2.4 | |

**TABLE 1.** Continued

| Patient characteristics | | All N=1,729 | | Guideline + n=888 (51.4%) | | Guideline - n=841 (48.6%) | | |
|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | p |
| **Previous thoracic surgery** | Yes | 101 | 5.8 | 56 | 6.3 | 45 | 5.4 | 0.074 |
| | No | 1,583 | 91.6 | 802 | 90.3 | 781 | 92.9 | |
| | Unknown/missing | 45 | 2.6 | 30 | 3.4 | 15 | 1.8 | |
| **Charlson comorbidity index** | 0 | 579 | 33.5 | 292 | 32.9 | 287 | 34.1 | 0.799 |
| | 1 | 535 | 30.9 | 274 | 30.9 | 261 | 31.0 | |
| | 2+ | 615 | 35.6 | 322 | 36.3 | 293 | 34.8 | |
| **Cardiac comorbidity** | Yes | 490 | 28.3 | 254 | 28.6 | 236 | 28.1 | 0.803 |
| | No | 1,239 | 71.7 | 634 | 71.4 | 605 | 71.9 | |
| **Pulmonary comorbidity** | Yes | 632 | 36.6 | 322 | 36.3 | 310 | 36.9 | 0.796 |
| | No | 1,097 | 63.4 | 566 | 63.7 | 531 | 63.1 | |
| **Clinical stage #** | cT1a-b (and T0 Tis) | 388 | 22.4 | 205 | 23.1 | 183 | 21.8 | 0.275 |
| | cT2a-b | 740 | 42.8 | 371 | 41.8 | 369 | 43.9 | |
| | cT3 | 446 | 25.8 | 221 | 24.9 | 225 | 26.8 | |
| | cT4 | 107 | 6.2 | 61 | 6.9 | 46 | 5.5 | |
| | Unknown/Tx /Missing | 48 | 2.8 | 30 | 3.4 | 18 | 2.1 | |
| **Tumor location** | Left lower lobe | 189 | 10.9 | 78 | 8.8 | 111 | 13.2 | <0.001 |
| | Left upper lobe | 362 | 20.9 | 154 | 17.3 | 208 | 24.7 | |

**TABLE 1.** Continued

| **Tumor location** | | All N=1,729 | | Guideline + n=888 (51.4%) | | Guideline - n=841 (48.6%) | | |
|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | p |
| | Left, unknown lobe | 215 | 12.4 | 94 | 10.6 | 121 | 14.4 | |
| | Right lower lobe | 185 | 10.7 | 108 | 12.2 | 77 | 9.2 | |
| | Right middle lobe | 33 | 1.9 | 24 | 2.7 | 9 | 1.1 | |
| | Right upper lobe | 431 | 24.9 | 259 | 29.2 | 172 | 20.5 | |
| | Right, unknown lobe | 314 | 18.2 | 171 | 19.3 | 143 | 17.0 | |

~ Diffuse Lung Capacity for Oxygen, percentage of expected
^ Forced Expiratory Volume in 1 second, percentage of expected
* American Society of Anesthesiologists score
[#]According to TNM 7 staging

**TABLE 2.** Guideline compliance by tumor location according to the Dutch and ESTS guidelines.

| Tumor location | No. | Dutch guideline (%) | ESTS guideline (%) |
|---|---|---|---|
| **RUL** | 431 | 60.1 | 71.9 |
| **RML** | 33 | 72.7 | 87.9 |
| **RLL** | 185 | 58.4 | 72.4 |
| **R unknown** | 314 | 54.5 | 68.8 |
| **LUL** | 362 | 42.5 | 80.1 |
| **LLL** | 189 | 41.3 | 84.1 |
| **L unknown** | 215 | 43.7 | 76.7 |
| **Total** | **1,729** | **51.4** | **75.4** |

RUL= right upper lobe
RML = right middle lobe
RLL = right lower lobe
LUL = left upper lobe
LLL = left lower lobe.
ESTS = European Society of Thoracic Surgeons

**TABLE 3.** Analysis of false negative mediastinoscopies (n=140).

| Lymph node station | Postoperative N2 disease (false negative mediastinoscopy) | Biopsied during mediastinoscopy | EUS / EBUS performed | On CT/ FDG-PET suspect | Other mediastal lymph node on CT/FDG-PET suspect |
|---|---|---|---|---|---|
| **2L** | 1 | 0 | 0 | 0 | 0 |
| **2R** | 5 | 4 | 1 | 0 | 1 |
| **3** | 1 | - | 1 | 0 | 0 |
| **4L** | 5 | 4 | 2 | 1 | 3 |
| **4R** | 18 | 16 | 8 | 6 | 6 |
| **5/6** | 53 | - | 23 | 16 | 15 |
| **7** | 47 | 41 | 27 | 14 | 15 |
| **8** | 12 | - | 3 | 2 | 5 |
| **9** | 11 | - | 3 | 0 | 5 |

CT = computed tomography
EBUS = endobronchial ultrasound
EUS = endoscopic ultrasound
FDG-PET = fluorodeoxyglucose positron emission tomography

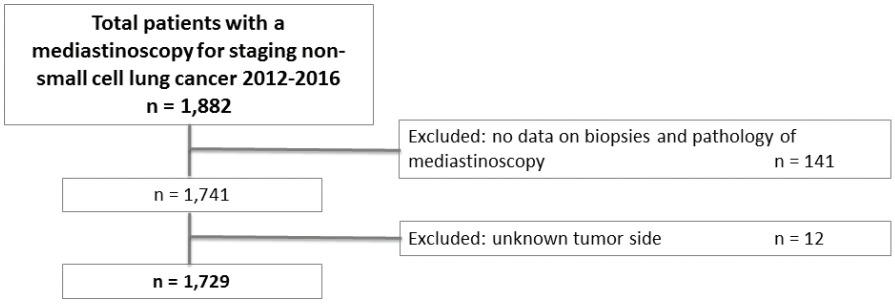


**FIGURE 1.** Flow chart of included and excluded patients.

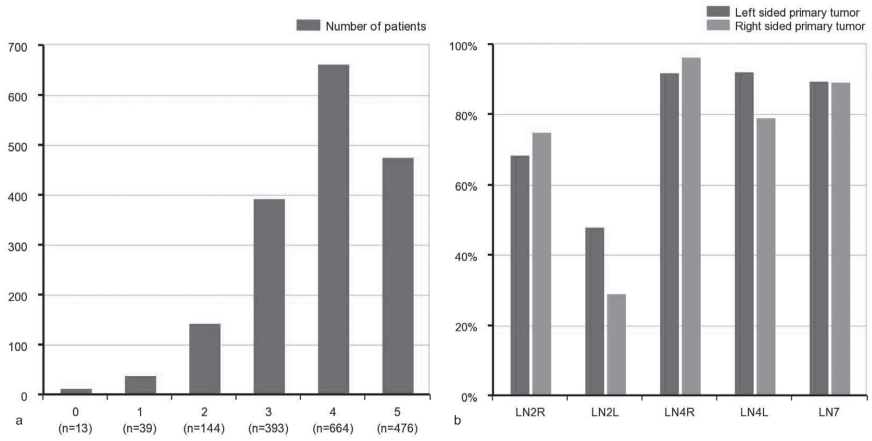


**FIGURE 2.** a) Number of biopsied lymph node stations at cervical mediastinoscopy (n=1,729). b) Percentage in which each lymph node station is biopsied during mediastinoscopy (n=1,729).

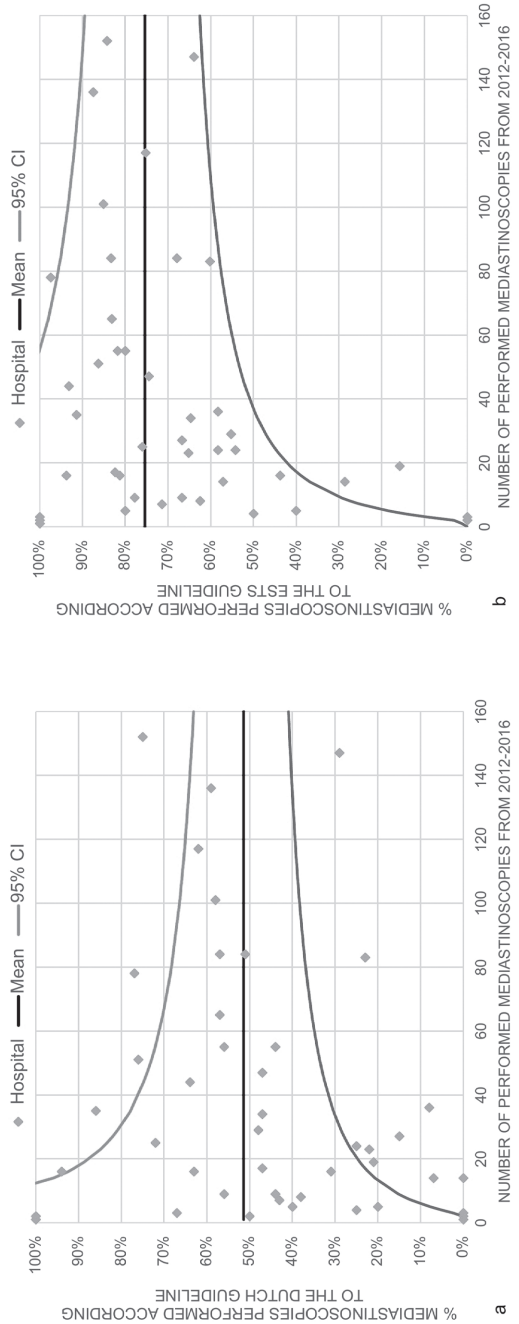


**FIGURE 3.** Variation between hospitals in the percentage of patients who underwent mediastinoscopy according to the criteria of a) the Dutch guideline b) the ESTS guideline. The black lines represent the national average, and the grey lines represent the 95% confidence intervals.

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# IMPACT OF HEALTH CARE ORGANIZATION ON SURGICAL LUNG CANCER CARE

7

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## ABSTRACT

### Objectives

Organization and governance of national healthcare might play an important role in decision-making and outcomes in patients with lung cancer. Both Denmark and the Netherlands have a high level of healthcare but a different financial coverage, governance and level of centralization. By using both national databases we analyzed the consequences of these differences on patterns of care and outcomes with a focus on morbidity, mortality and clinical staging.

### Materials and methods

General numbers on both healthcare systems were requested. All patients who had surgery for lung cancer from 2013 to 2016 were included. Mortality, morbidity and clinical staging were analyzed for patients with NSCLC without metastases, only one operation and no neo-adjuvant therapy.

### Results

In 2016 annual budget as share of gross national product was 10.4% for both countries. In Denmark 4 hospitals performed lung surgery in 2016, compared to 43 hospitals in the Netherlands. We included 4,030 Danish and 8,286 Dutch patients. In the subgroup 30-day mortality was 1.5% in Denmark compared to 1.9% in the Netherlands. The percentage of patients with a complicated course was 24.4% and 34.8% respectively ($p<0.05$). Accuracy between cTNM and pTNM was 53.0% in Denmark and 52.9% in the Netherlands.

### Conclusion

Surgery for lung cancer is at a high level in both countries, reflected by low mortality-rates. Centralization has been implemented successfully in Denmark, which might explain the lower rate of patients with a complicated post-operative course, although different definitions preclude firm conclusions. In both countries correct clinical staging of lung cancer remains a challenge.

## INTRODUCTION

Lung cancer is the most common cause of cancer related death worldwide. Accurate diagnosis and staging are crucial to direct the individual patient towards the optimal treatment. Ideally, all patients with lung cancer should be diagnosed, staged and treated in a uniform fashion. However, it is known that socio-economic status, gender, race and multidisciplinary tumor board discussion, are all factors that have the potential to influence the probability to receive a certain treatment.[1-4] In addition, to what extent the organization of national healthcare and governance might have an impact on daily practice and outcomes for patients with lung cancer, is currently unknown. Although both Denmark and the Netherlands have high quality national healthcare systems according to the Euro Health Consumer Index (EHCI)[5], healthcare organization differs significantly on several aspects: (1) Financial coverage: in Denmark healthcare is financed from taxes for all inhabitants. In contrast, in the Netherlands, healthcare insurance is obligatory and inhabitants pay insurance costs to insurance companies. (2) Governance: in both countries, politicians govern the healthcare system. In the Netherlands, however, the hospitals (and doctors) are independent caregivers, where insurance companies can contract healthcare for their patients. (3) Centralization: one of the results of the difference in governance is that lung cancer care (including surgery) is rigorously centralized in Denmark (4 hospitals performing lung surgery in 2016), a process that has just started in the Netherlands (from 79 in 2005 to 42 hospitals performing lung surgery in 2018).

Both Denmark and the Netherlands have a national audit in which data regarding lung cancer is systematically collected.[6,7] To improve lung cancer care in Denmark, the Danish Lung Cancer Group (DLCG) was founded in 1991 and the Danish Lung Cancer Registry (DLCR) opened for registration in 2000.[6] In the Netherlands, a database on lung cancer surgery was initiated in 2011 (Dutch Lung Surgery Audit (DLSA)). To cover and audit all aspects of lung cancer, the radiotherapists and the pulmonologists joined the audit in 2016 and 2017 respectively, and from then on the audit is called Dutch Lung Cancer Audit (DLCA, and DLCA-S for the surgical part of the database).[7,8]

In this study, the aim was to analyze the differences in healthcare organization and governance and the possible impact on daily practice and outcome, with a focus on morbidity, mortality and clinical staging.

## MATERIALS AND METHODS

### General data and patients

To compare both countries in general, variables such as lung cancer incidence, number of inhabitants, lung cancer resection rates and life expectancy were requested from the Danish and Dutch Cancer Registries, and from the Organisation for Economic Co-operation and Development (OECDstat).

All patients who had surgery for lung cancer from January 1st 2013, until December 31st 2016 were identified (Group I) and after comparing data definitions, predefined data were compared.

### Outcomes

At first, general characteristics of all patients who had surgery for lung cancer from January 1st 2013, until December 31st 2016 were analyzed (Group I). After selection, a subgroup (Group II) was defined to enable proper comparison of patients from both countries, without possible bias from previous (neo-adjuvant) therapy or metastases. This group consisted of patients with primary surgery for NSCLC, without neo-adjuvant therapy and without metastases at time of diagnosis (see Figure 1: Flowchart). For patients in Group II, outcomes were analyzed such as morbidity, mortality and risk adjusted mortality rates (RAMR), and the agreement between clinical stage (cTNM) and pathological stage (pTNM), as a measure of clinical staging accuracy in patients with NSCLC.

*Statistical analysis*

Descriptive statistics were used for all analysis. Chi-square tests were used to analyze dichotomous variables. To calculate the RAMR for both countries, the expected mortality per country was calculated using multivariable logistic regression analysis. Factors included in the regression model were sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, histopathology, type of resection, type of entry in the thorax and year of surgery. Histopathology was removed from the definitive correction model because it was not significant in multivariable analysis. Statistical analysis was performed in SPSS version 25.

## RESULTS

In Table 1, the basic characteristics of lung cancer care in Denmark and the Netherlands in 2016 are presented. The number of inhabitants was approximately 3 times higher in the Netherlands and life expectancy at birth was comparable. Incidences of airway tract cancer were slightly higher in Denmark. In 2016, there were 4 hospitals performing lung surgery in Denmark (average number of resections per hospital per year: 252), compared to 43 hospitals in the Netherlands (average number of resections per hospital per year: 48). The annual budget for health care as a share of gross national product was exactly the same for both countries in 2016: 10.4%. Resection rates for NSCLC were comparable in both countries.

### Outcomes Group I

Between January 1st 2013 and December 31st 2016, a total of 4,030 patients with resected lung cancer were registered in the Danish DLCR and 8,286 patients in the Dutch DLCA-S (Supplement 1). The mean age at time of surgery differed slightly between Denmark (68 years) and the Netherlands (65.6 years), however age-distribution was different ($p<0.05$). In Denmark 54.2% of patients were younger than 70 years compared with 62.5% in the Netherlands. Most surgically treated patients had clinical stage IA (40.2% in Denmark and 35.8% in the Netherlands). Primary surgery in patients with clinical N2 disease was uncommon: 3.6% in Denmark and 4.9% in the Netherlands. Neo-adjuvant treatment was used in 4.6% of patients in Denmark and 6.8% of patients in the Netherlands ($p<0.05$). Surgery was predominantly performed by thoracoscopic approach in both countries: 64.7% in Denmark and 56.7% in the Netherlands ($p<0.05$). In the Netherlands, however, in 10.9% of patients a thoracoscopy was converted to an open procedure (conversion rate in Denmark is unknown; converted procedures are recorded as thoracotomy). When analyzing type of resection, lobectomy was performed in 71.5% in Denmark and 74.8% in the Netherlands. In Denmark, 17.0% of patients had a wedge resection compared to 8.5% in the Netherlands, and 10.9% of the Danish patients had two or more surgical procedures compared to 2.4% in the Netherlands ($p<0.05$).

### Outcomes Group II

Table 2 presents the characteristics of Group II. In Denmark, 2,489 patients were registered who met these criteria, in the Netherlands 5,449 patients. In this selected group, clinical stage IA NSCLC remained the most frequent

indication for surgery (42.5% versus 39.8% for Denmark and the Netherlands, respectively). Primary surgery for stage IIIA and IIIB comprised 7.8% of all surgical patients in Denmark, compared with 9.1% in the Netherlands. In Denmark 63.8% of patients were operated by thoracoscopic approach, 59.1% of patients in the Netherlands was operated this way ($p<0.05$). However, in 11.9% of patients operations were started thoracoscopically in the Netherlands but were then converted to an open procedure (converted procedures recorded as thoracotomy in Denmark). Lobectomy remained the preferred procedure in this subgroup: 81.2% of the Danish and 81.4% of the Dutch patients underwent lobectomy. Wedge resection was the performed procedure in 8.1% of patients in Denmark and in 3.2% of patients in the Netherlands.

In Table 3 the recorded morbidity and mortality of Group II is presented: in Denmark the percentage of patients with a complicated course after surgery was 24.4%, the 30-day mortality was 1.5% and the risk adjusted mortality 1.7% (95%-CI: 1.3-2.4%). For the Netherlands, these numbers were 34.8%, 1.9% and 1.8% (95%-CI: 1.4-2.2%), respectively ((risk adjusted) mortality: not significant, complicated course: $p<0.05$).

Table 4 presents the clinical and pathological TNM for Group II. Accuracy of staging is highest in early stage lung cancer: in Denmark, this was 59.2% for stage IA and 56.5% for stage IB, in the Netherlands 65.9% and 49.8%, for stage IA and IB, respectively. Overall accuracy of the clinical staging process was 53.0% in Denmark and 52.9% in the Netherlands.

## DISCUSSION

Clinical auditing was designed to assess quality of medical care and to benchmark treatment outcome. It can be used to analyze variation in patterns of care and outcomes. Benchmarking can be used as a feedback tool for hospitals or individual caregivers to provide insight in ways to improve quality of care.[16-19] This analysis is the first using two national registries (DLCR and DLCA-S) to compare patterns of care and outcomes for lung cancer patients treated with surgery. Both countries are located in Western Europe and have access to high quality health care, but have a different national healthcare organization in terms of financial coverage, governance and level of centralization. Where lung cancer surgery is highly centralized in Denmark, centralization in the Netherlands is an ongoing process. Despite the differences in financial coverage and governance, it is

remarkable that the annual budget for health care as share of gross national product is exactly the same in both countries. Several findings from this analysis deserve a closer look.

**Centralization**

In Denmark, lung surgical operations were performed in 4 hospitals during the entire inclusion period. In the Netherlands, there were 43 hospitals performing lung surgical operations in 2016 (last year of inclusion period). This leads to a considerable variety in number of procedures per hospital per year: an average of 252 procedures per hospital per year in Denmark, compared to 48 in the Netherlands during the analyzed period. Several studies report improved outcomes in high volume centers compared to low volume centers, however, the cut-off value for volume currently is an ongoing subject of debate.[20-24] It is hard to conclude from our data whether differences in outcomes, as discussed in the following paragraphs, are in more or lesser extent attributable to the different level of centralization.

**Characteristics Group I**

A relative lower number of patients operated for NSCLC were included in the Dutch registration when compared with Denmark. There are several possible explanations for this finding. First, registration of pulmonary procedures was voluntary at the beginning of the analyzed period in the Netherlands. However, it became obligatory for all institutes performing lung surgery in 2015, resulting in an increased number of registered resections in the DLCA-S (from 1,870 in the year 2013 to 2,349 in 2016). Secondly, the slightly lower incidence of lung cancer in the Netherlands might be part of the explanation why there were not a 3-fold of patients registered in the DLCA-S compared to the DLCR. Another possible explanations is that patients in the Netherlands presented in higher clinical stages, not amenable for surgery. Finally, radiotherapy might have been the preferred choice of treatment in (elderly) patients instead of surgery. These possible explanations warrant further research by analyzing radiotherapy and pulmonology data.

When looking at age, in Denmark 54.2% of patients were younger than 70 years, compared to 62.5% of patients in the Netherlands. The distribution between age categories differed significantly between the two countries, probably explained by the higher centralization rate in Denmark, resulting in more resections for patients with higher ages.[25] In addition, the use of

radiotherapy instead of surgery in higher aged patients might also contribute to this finding.

**Resection type**

In Denmark, 17% of patients were treated primarily with a wedge resection, predominantly for diagnostic purposes or metastasectomies, which appeared to be primary lung cancer on final pathological examination. In some of these patients, the wedge resection was followed by a completion lobectomy, explaining the high number of patients that had multiple surgeries in the Danish database. However, even after exclusion of these patients, still 8.1% of patients was treated by wedge resection for NSCLC (Group II) in Denmark. It would be interesting to know patient characteristics and long-term survival of these patients, as a wedge resection is considered an inferior treatment when compared to anatomical parenchymal resections.[26,27]

**Characteristics Group II**

When analyzing Group II in more detail, clinical stage IA NSCLC was the most frequent indication for surgery and video-assisted thoracic surgery (VATS) was the preferred surgical approach in both countries. Although minimally invasive surgery does not improve survival compared to open procedures, its benefits are shorter length of stay, less postoperative pain and a better quality of life in the first year after surgery.[28-32]

**Morbidity and mortality Group II**

In Denmark, 24.4% of the patients had a complicated post-operative course compared to 34.8% in the Netherlands ($p<0.05$). Regarding the type of complications, pneumonia, wound infection, empyema, fistula, atelectases, atrial fibrillation and pulmonary embolism were recorded more frequently in the Netherlands than in Denmark ($p<0.05$). Although data definitions were compared, it is difficult to interpret these data because details regarding definitions of complications are lacking. For example, it is unclear whether the definitions and diagnosis of pneumonia or wound infection are the same in Denmark and the Netherlands. One clear difference in definition is prolonged air leakage: in Denmark this is defined as persistent air leakage longer than 7 days post-operatively, where in the Netherlands this is 5 days. A cardiopulmonary morbidity rate of 18.7% was found by Brunelli et al analyzing the European Society of Thoracic Surgeons (ESTS) database, and

although this group published the data definitions of the Society of Thoracic Surgeons (STS) and ESTS database extensively in an earlier publication, it is still very difficult to compare their reported morbidity rates with these found from our analysis due to the lack of well-defined data definitions.[33,34] Although there was an absolute difference in 30-day mortality of 0.4% in favor of Denmark compared with the Netherlands (p=0.28), risk adjusted mortality rates narrowed this difference (1.7 versus 1.8% respectively, not significant). Both mortality rates compare favorable with those reported in the literature. In a large retrospective ESTS analysis of 47,960 patients who underwent an anatomic lung resection from 2007-2015, the 30-day mortality was 2.7%.[34] When interpreting these data, however, one should realize that the nature of the data from both our dataset as well as the one used by the ESTS (e.g. retrospective analysis, voluntary participation (ESTS), not all hospitals (beginning of the DLCA-S)/countries (ESTS) participating), is subject to bias and true numbers may differ.

**Accuracy of clinical staging Group II**

The calculated overall staging accuracy of surgically treated NSCLC was 53.0% in Denmark and 52.9% in the Netherlands, with staging of early stages being more accurate. Although these numbers can be considered very low, other authors have previously reported numbers of this range.[35-37] In Denmark, an accuracy of 91.3% has been reported previously.[6] The algorithm that was used to calculate this impressive percentage assumed accordance was reached when there was no change of treatment for the patient. A change of treatment was made in those patients in whom a resectable tumor turned out to be T4 pathologically, when unforeseen N2 or N3 nodes were discovered or when unexpected metastases were proven in the pathological TNM. The problem with this algorithm is that it assumes that there is no difference in treatment between a T1a or T3, or a N0 or N1. This used to be true when only surgical treatment could be used as treatment in resectable NSCLC. Currently there are many emerging therapies, from stereotactic ablative body radiotherapy (SABR) in operable stage I disease, chemoradiotherapy as induction therapy in locally advanced NSCLC, to new developments in using immunotherapy as neo-adjuvant therapy. It is therefore of utmost importance to obtain a correct clinical stage before any treatment starts We do believe that difficulty in clinical staging will be an important limitation in current ongoing studies that evaluate neo-adjuvant therapy. From a Dutch cohort, it was already shown

that in surgically treated clinical stage I disease, more than 22% of patients was upstaged to a pathological stage II or higher.[38]

**Limitations**

The most important limitation is that comparing two national databases means comparing two sets with different definitions of endpoints. Databases are developed and designed for benchmarking purposes, and to compare hospitals or caregivers within a country. When comparing two countries, it is very important that data definitions correspond, which is unclear in some of the parameters in this study because of lack of definition. Another important limitation is that it is not clear what impact governance and centralization have on lung cancer care: survival data are lacking, so the effect of centralization could not be extracted from this dataset. This merits further research, particularly since recent studies from the UK and Germany report on shorter length of stay and lower risk of re-admission and death in high volume centers.[21,22,24] It is interesting to evaluate the different patterns of care in both countries, but differences in datasets hamper drawing firm conclusions on who perform best, and what recommendations would improve health care. Finally, the way data is gathered in the databases can cause unreliable results: in Denmark data registration is linked to the financial administration, assuming hospitals have a correct financial system and thus registered data are correct. In the Netherlands physicians are responsible for data registration and do it themselves or have supporting staff that register the data. Data-verification in the Netherlands is done by an external organization.[7,39] Both ways of data collection have their own flaws and might cause bias.

**Future Perspectives**

Due to different data definitions used in both audits, it is very difficult to draw conclusions from the presented data. To compare healthcare and outcome between countries, to identify positive and negative outliers, and learn from each other how to improve outcomes in surgical lung cancer care, we recommend applying comparable data definitions for outcomes and complications or even synchronize registries throughout Europe (and if possible the world).

## CONCLUSION

In this study we compared surgical lung cancer care in two western European countries with a high level of healthcare by using their respective national databases. Surgery for lung cancer is of good quality in both Denmark and the Netherlands, which is demonstrated by low mortality numbers. Centralization has been implemented successfully in Denmark, which might explain the lower rates of patients with a complicated course, although different definitions of endpoints in the databases preclude firm conclusions. In both Denmark and the Netherlands correct clinical staging of lung cancer remains a challenge. Implementation of uniform definitions of clinical endpoints on an international level is a prerequisite for comparing datasets. Relating organization and governance of national healthcare systems to clinically relevant endpoints may very well deliver the necessary tools to improve surgical lung cancer care on a global scale.

**TABLE 1.** Basic characteristics of lung cancer care in Denmark and the Netherlands in 2016

| | **Denmark** | **Netherlands** |
|---|---|---|
| Number of inhabitants[9, 10] | 5,707,251 | 16,979,120 |
| Life expectancy female at birth | 82.8 years | 83.2 years |
| Life expectancy male at birth | 79.0 years | 80.0 years |
| Annual budget for health care as share of gross national product[11] | 10.4% | 10.4% |
| Number of practicing physicians in (head count, 2015) | 20,902 | 59,073 |
| Number of hospitals performing lung surgery[12,13] | 4 | 43 |
| Average volume per hospital per year* (median (min-max)) | 252 (144-324) | 48 (25 –109) |
| Incidence airway tract cancer (lung + trachea + mesothelioma + thymus)/100.000[14,15] | 90 | 79 |
| Incidence lung cancer overall/100.000[14,15] | 82 | 75 |
| Incidence NSCLC/100.000[12,15] | 68 | 55 |
| Resection rate NSCLC[12,13] | 23.2% | 22.8% |

* Calculated over 2013-2016
NSCLC – Non-Small Cell Lung Cancer

**TABLE 2.** Operations on patients with NSCLC, no metastasis, one operation and no neo-adjuvant therapy 2013-2016 (Group II)

| | | Denmark | | Netherlands | | p-value |
|---|---|---|---|---|---|---|
| | | n | % | n | % | $\chi^2$ |
| **Total** | | 2,489 | 100.0 | 5,449 | 100.0 | |
| **Year of surgery** | 2013 | 486 | 19.5 | 1,179 | 21.6 | < 0.05 |
| | 2014 | 593 | 23.8 | 1,118 | 20.5 | |
| | 2015 | 668 | 26.8 | 1,551 | 28.5 | |
| | 2016 | 742 | 29.8 | 1,601 | 29.4 | |
| **Gender** | Female | 1,207 | 48.5 | 2,414 | 44.3 | < 0.05 |
| | Male | 1,282 | 51.5 | 3,035 | 55.7 | |
| **Age in categories** | <=59 | 380 | 15.3 | 1,088 | 20.0 | < 0.05 |
| | 60-69 year | 886 | 35.6 | 2,109 | 38.7 | |
| | 70-79 year | 985 | 39.6 | 1,922 | 35.3 | |
| | >=80 year | 238 | 9.6 | 330 | 6.1 | |
| **ECOG score** | ecog 0 | 1,505 | 60.5 | 2,813 | 51.6 | < 0.05 |
| | ecog 1 | 621 | 24.9 | 1,331 | 24.4 | |
| | ecog 2+ | 122 | 4.8 | 176 | 3.2 | |
| | unknown/missing | 241 | 9.7 | 1,129 | 20.7 | |
| **Clinical TNM stage*** | Stage IA | 1,057 | 42.5 | 2,168 | 39.8 | < 0.05 |
| | Stage IB | 630 | 25.3 | 1,205 | 22.1 | |
| | Stage IIA | 295 | 11.9 | 877 | 16.1 | |
| | Stage IIB | 312 | 12.5 | 699 | 12.8 | |
| | Stage IIIA | 180 | 7.2 | 471 | 8.6 | |
| | Stage IIIB | 15 | 0.6 | 29 | 0.5 | |
| **Clinical T stage** | T1a-b (+ T0-is) | 1,131 | 45.4 | 2,435 | 44.7 | 0.91 |
| | T2a-b | 932 | 37.4 | 2,054 | 37.7 | |
| | T3 | 359 | 14.4 | 813 | 14.9 | |
| | T4 | 67 | 2.7 | 147 | 2.7 | |
| **Clinical N stage** | N0 | 2,185 | 87.8 | 4,487 | 82.3 | < 0.05 |
| | N1 | 238 | 9.6 | 782 | 14.4 | |
| | N2 | 56 | 2.2 | 164 | 3.0 | |
| | N3 | 10 | 0.4 | 16 | 0.3 | |
| **Histopathology** | Adenocarcinoma | 1,459 | 58.6 | 3,204 | 58.8 | < 0.05 |

**TABLE 2.** Continued

| | | Denmark | | Netherlands | | p-value |
|---|---|---|---|---|---|---|
| | | n | % | n | % | $\chi^2$ |
| | Squamous cell carcinoma | 720 | 28.9 | 1,979 | 36.3 | |
| | Different NSCLC | 310 | 12.5 | 266 | 4.9 | |
| **Type of entry thorax** | Thoracotomy | 901 | 36.2 | 1,462 | 26.8 | < 0.05** |
| | VATS/RATS | 1,588 | 63.8 | 3,223 | 59.1 | |
| | Conversion** | - | - | 649 | 11.9 | |
| | Unknown/missing | 0 | 0.0 | 115 | 2.2 | |
| **Type of resection** | Wedge resection | 201 | 8.1 | 174 | 3.2 | < 0.05 |
| | Segmentectomy | 62 | 2.5 | 101 | 1.9 | |
| | Lobectomy | 2,024 | 81.2 | 4,437 | 81.4 | |
| | Bilobectomy | 101 | 4.1 | 322 | 5.9 | |
| | Pneumonectomy | 101 | 4.1 | 415 | 7.6 | |

* According to TNM-7
** In the Danish data the conversion rate is unknow, conversion of a VATS/RATS was registered as thoracotomy. For calculating the p-value, conversions in the Dutch data are counted in the group thoracotomy.

ECOG – Eastern Cooperative Oncology Group Performance Score
NSCLC – Non-Small Cell Lung Cancer
VATS – Video-Assisted Thoracoscopic Surgery
RATS – Robotic-Assisted Thoracoscopic Surgery

**TABLE 3.** Mortality and morbidity for Group II

| | Denmark | | Netherlands | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | $\chi^2$ |
| **Total** | 2,489 | 100.0 | 5,449 | 100.0 | |
| **Mortality (30 days)** | 38 | 1.5 | 102 | 1.9 | 0.28 |
| **Complicated course (30 days)*** | 608 | 24.4 | 1,894 | 34.8 | < 0.05 |
| **Bleeding with reoperation** | 29 | 1.2 | 65 | 1.2 | 0.92 |
| **Prolonged air leakage**** | 229 | 9.2 | 456 | 8.4 | 0.22 |
| **Pneumonia** | 132 | 5.3 | 603 | 11.1 | < 0.05 |
| **Wound infection** | 6 | 0.2 | 39 | 0.7 | < 0.05 |
| **Empyema** | 22 | 0.9 | 90 | 1.7 | < 0.05 |
| **Bronchopleural fistula** | 2 | 0.1 | 18 | 0.3 | < 0.05 |
| **Atelectasis** | 24 | 1.0 | 143 | 2.6 | < 0.05 |
| **Myocardial ischemia/ infarction** | 6 | 0.2 | 23 | 0.4 | 0.21 |
| **Atrial fibrillation** | 91 | 3.7 | 266 | 4.9 | < 0.05 |
| **Pulmonary embolism** | 5 | 0.2 | 42 | 0.8 | < 0.05 |

* Patients can have multiple complications
** Prolonged air leakage Denmark = more than 7 days, NL = more than 5 days

**TABLE 4.** Comparison between clinical stage and pathological stage for Group II

| **Denmark** | | **pStage** | | | | | | **Total** | **% correct** |
|---|---|---|---|---|---|---|---|---|---|
| | | Stage IA | Stage IB | Stage IIA | Stage IIB | Stage IIIA | Stage IIIB | | |
| **cStage** | Stage IA | 626 | 271 | 72 | 43 | 45 | 0 | 1,057 | 59.2 |
| | Stage IB | 81 | 356 | 87 | 51 | 54 | 1 | 630 | 56.5 |
| | Stage IIA | 19 | 54 | 109 | 36 | 76 | 1 | 295 | 36.9 |
| | Stage IIB | 18 | 41 | 48 | 137 | 65 | 3 | 312 | 43.9 |
| | Stage IIIA | 18 | 17 | 16 | 35 | 90 | 4 | 180 | 50.0 |
| | Stage IIIB | 3 | 2 | 5 | 2 | 2 | 1 | 15 | 6.7 |
| **Total** | | 765 | 741 | 337 | 304 | 332 | 10 | 2,489 | 53.0 |

| **Netherlands** | | **pStage** | | | | | | **Total** | **% correct** |
|---|---|---|---|---|---|---|---|---|---|
| | | Stage IA | Stage IB | Stage IIA | Stage IIB | Stage IIIA | Stage IIIB | | |
| **cStage** | Stage IA | 1,429 | 419 | 151 | 48 | 118 | 3 | 2,168 | 65.9 |
| | Stage IB | 160 | 600 | 223 | 91 | 128 | 3 | 1,205 | 49.8 |
| | Stage IIA | 92 | 158 | 326 | 142 | 153 | 6 | 877 | 37.2 |
| | Stage IIB | 55 | 64 | 116 | 292 | 170 | 2 | 699 | 41.8 |
| | Stage IIIA | 36 | 38 | 63 | 91 | 231 | 12 | 471 | 49.0 |
| | Stage IIIB | 4 | 3 | 6 | 7 | 6 | 3 | 29 | 10.3 |
| **Total** | | 1,776 | 1,282 | 885 | 671 | 806 | 29 | 5,449 | 52.9 |

cStage – clinical stage
pStage – pathological stage

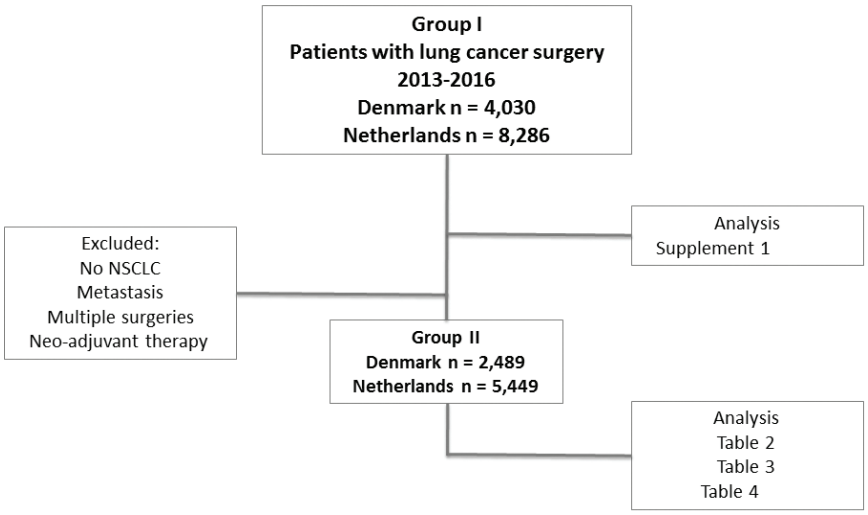


**FIGURE 1.** Flowchart of study population and analyses.

**SUPPLEMENT 1.** Operations on patients with known age and sex and resection of lung cancer of any type 2013-2016 (Group I)

| | | Denmark | | Netherlands | | p-value |
|---|---|---|---|---|---|---|
| | | n | % | n | % | $\chi^2$ |
| **Total** | | 4,030 | 100.0 | 8,286 | 100.0 | |
| **Year of surgery** | 2013 | 768 | 19.1 | 1,870 | 22.6 | < 0.05 |
| | 2014 | 1,140 | 28.3 | 1,767 | 21.3 | |
| | 2015 | 1,030 | 25.6 | 2,300 | 27.8 | |
| | 2016 | 1,092 | 27.1 | 2,349 | 28.3 | |
| **Gender** | Female | 1,887 | 46.8 | 3,735 | 45.1 | 0.07 |
| | Male | 2,143 | 53.2 | 4,551 | 54.9 | |
| **Age** | =< 59 years | 716 | 17.8 | 1,986 | 24.0 | < 0.05 |
| | 60-69 years | 1,467 | 36.4 | 3,187 | 38.5 | |
| | 70-79 years | 1,532 | 38.0 | 2,698 | 32.6 | |
| | => 80 years | 315 | 7.8 | 415 | 5.0 | |
| **ECOG score** | Ecog 0 | 2,329 | 57.8 | 4,188 | 50.5 | < 0.05 |
| | Ecog 1 | 972 | 24.1 | 2,001 | 24.1 | |
| | Ecog 2+ | 209 | 5.2 | 282 | 3.4 | |
| | Unknown/ missing | 520 | 12.9 | 1,815 | 21.9 | |
| **Clinical TNM stage*** | Stage 0/Occult | 16 | 0.4 | 157 | 1.9 | < 0.05 |
| | Stage IA | 1,621 | 40.2 | 2,969 | 35.8 | |
| | Stage IB | 859 | 21.3 | 1,504 | 18.2 | |
| | Stage IIA | 402 | 10.0 | 1,074 | 13.0 | |
| | Stage IIB | 432 | 10.7 | 982 | 11.9 | |
| | Stage IIIA | 324 | 8.0 | 833 | 10.1 | |

**SUPPLEMENT 1.** Continued

| | | Denmark | | Netherlands | | p-value |
|---|---|---|---|---|---|---|
| | | n | % | n | % | $\chi^2$ |
| | Stage IIIB | 37 | 0.9 | 86 | 1.0 | |
| | Stage IV | 181 | 4.5 | 86 | 1.0 | |
| | Unknown/ missing | 158 | 3.9 | 595 | 7.2 | |
| **Clinical T stage** | T1a-b (+ T0-is) | 1,827 | 45.3 | 3,535 | 42.7 | < 0.05 |
| | T2a-b | 1,352 | 33.5 | 2,729 | 32.9 | |
| | T3 | 566 | 14.0 | 1,297 | 15.7 | |
| | T4 | 165 | 4.1 | 323 | 3.9 | |
| | Unknown/Tx/ Missing | 120 | 3.0 | 402 | 4.9 | |
| **Clinical N stage** | N0 | 3,335 | 82.8 | 6,445 | 77.8 | < 0.05 |
| | N1 | 360 | 8.9 | 1,063 | 12.8 | |
| | N2 | 144 | 3.6 | 405 | 4.9 | |
| | N3 | 33 | 0.8 | 50 | 0.6 | |
| | Unknown/ missing | 158 | 3.9 | 323 | 3.9 | |
| **Histopathology** | Small cell carcinoma | 55 | 1.4 | 85 | 1.0 | < 0.05** |
| | Adenocarcinoma | 2,209 | 54.8 | 4,190 | 50.6 | |
| | Squamous cell carcinoma | 985 | 24.4 | 2,405 | 29.0 | |
| | Different NSCLC | 739 | 18.3 | 813 | 9.8 | |
| | Benign | 0 | 0.0 | 473 | 5.7 | |
| | Missing/other | 42 | 1.0 | 320 | 3.9 | |
| **Neoadjuvant treatment** | No | 3,845 | 95.4 | 7,726 | 93.2 | < 0.05 |
| | Yes | 185 | 4.6 | 560 | 6.8 | |

**SUPPLEMENT 1.** Continued

| | | Denmark | | Netherlands | | p-value |
|---|---|---|---|---|---|---|
| | | n | % | n | % | $\chi^2$ |
| **Type of entry thorax** | Thoracotomy | 1,422 | 35.3 | 2,506 | 30.2 | < 0.05*** |
| | VATS / RATS | 2,606 | 64.7 | 4,698 | 56.7 | |
| | Conversion rate*** | - | - | 905 | 10.9 | |
| | Unknown/ missing | 2 | 0.0 | 177 | 2.2 | |
| **Type of resection** | Explorative thoracotomy | 64 | 1.6 | 123 | 1.5 | < 0.05 |
| | Wedge resection | 684 | 17.0 | 701 | 8.5 | |
| | Segmentectomy | 106 | 2.6 | 187 | 2.3 | |
| | Lobectomy | 2,881 | 71.5 | 6,195 | 74.8 | |
| | Bilobectomy | 150 | 3.7 | 469 | 5.7 | |
| | Pneumonectomy | 139 | 3.4 | 602 | 7.3 | |
| | Unknown/ missing/different | 6 | 0.1 | 9 | 0.1 | |
| **More than 1 surgery?** | Yes | 439 | 10.9 | 202 | 2.4 | < 0.05 |
| | No | 3,591 | 89.1 | 8,084 | 97.6 | |

*According to TNM-7
** For calculating the p-value the groups 'benign' and 'missing/other' were merged.
*** In the Danish data the conversion rate is unknown, conversion of a VATS/RATS was registered as thoracotomy. For calculating the p-value, conversions in the Dutch data are counted in the thoracotomy group

ECOG – Eastern Cooperative Oncology Group Performance Score
NSCLC – Non-Small Cell Lung Cancer
VATS – Video-Assisted Thoracoscopic Surgery
RATS – Robotic-Assisted Thoracoscopic Surgery

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# CLINICAL STAGING OF NSCLC: CURRENT EVIDENCE AND IMPLICATIONS ON ADJUVANT CHEMOTHERAPY.

8

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## ABSTRACT

Survival of all non-small cell lung cancer (NSCLC) patients is disappointing, with a 5-year survival of 18%. Staging NSCLC patients is crucial because it determines the choice of treatment and prognosis. Clinical staging is a complex process that comes with many challenges and with low accuracy between the clinical and pathological stage. Treatment modalities for stage I–III NSCLC consist of surgical resection, radiotherapy and chemotherapy. This review describes the current evidence on staging and the implications on adjuvant chemotherapy. For stage I disease, staging is most accurate. Primary treatment consists of surgery or stereotactic ablative radiotherapy. When a patient has stage II disease, staging is less accurate because more diagnostic modalities are necessary to stage the mediastinal lymph nodes. Surgery remains the primary treatment modality and platinum-based adjuvant chemotherapy gives a 4% 5-year survival benefit. Staging patients with stage III disease is difficult because of the heterogeneity of the patients. It should be decided if a patient has potentially resectable disease with or without risk of incomplete resection. Induction therapy with chemo(radio) therapy followed by surgical resection or definitive chemoradiotherapy are the treatments of choice. The 5-year survival can reach 44% in selected patients. Decisions in staging and treating patients with NSCLC should be made by a multidisciplinary team with sufficient expertise in all aspects of staging and treatment.

## INTRODUCTION

Lung cancer causes most cancer-related deaths worldwide.[1–3] Clinical staging of non-small cell lung cancer (NSCLC) is difficult. Although separate diagnostic modalities have high sensitivity and specificity,[4] comparing the clinical stage (cTNM) and pathological stage (pTNM) has an accuracy that is generally low, between 50– 60%.[5–14] Survival of NSCLC remains disappointing with a 5-year survival of 18% for all NSCLC patients, and a 60–80% survival in stage I patients after an anatomical resection.[15,16] It is important to have a correct clinical stage because this determines the choice of initial treatment and thus survival. With a correct clinical stage unnecessary morbidity and mortality of treatment can be minimized. Stage I patients, with tumors up to 5 cm and no lymph node involvement, are usually treated with monotherapy, being either resection or stereotactic ablative radiotherapy (SABR), most often used in patients unfit for surgery. In NSCLC stage II, therapy usually consists of primary treatment, (e.g. resection), followed by adjuvant chemotherapy. In patients with locally advanced NSCLC (stage III) induction chemo- or radiotherapy followed by resection or definitive combined modality treatment (concurrent or sequential chemoradiation) is the standard. In patients with no resection and hence no definitive pathological TNM stage, adjuvant treatment is chosen based on the clinical TNM stage. This opinionated, narrative review will discuss the role of clinical staging of NSCLC and the implications on adjuvant chemotherapy.



## THE BENEFIT OF ADJUVANT CHEMOTHERAPY IN PATIENTS WITH RESECTABLE NSCLC

The results of the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis have largely determined the current vision on the use of adjuvant chemotherapy in patients with NSCLC. This study, published by Pignon and colleagues in 2008 in *Journal of Clinical Oncology*, showed a survival benefit for patients receiving platinum-based chemotherapy after complete resection of stage II or stage III NSCLC. It showed a 5.4% benefit in 5-year survival when cisplatin-based adjuvant chemotherapy was given, an effect that was even higher in patients with a higher socio- economic status.[17] A Cochrane review published in 2015 on adjuvant chemotherapy after resected NSCLC, comprising 26 trials and more than 11,000 patients, confirmed these findings and demonstrated the clear significant benefit of adjuvant chemotherapy for patients receiving chemotherapy after radical



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surgery or after surgery combined with radiotherapy. This meta-analysis shows a significant 4% improvement in 5-year overall survival, increasing survival from 60–64% for the whole group of patients. The trials included in this analysis mainly used cisplatin-based chemotherapy, and in some included articles tegafur/uracil was used as the chemotherapeutic agent.[18] Neoadjuvant chemotherapy is reserved for patients with locally advanced NSCLC, since there is no evidence that it plays a beneficiary role in patients with stage I–II NSCLC according to the NATCH trial.[19]

## DETERMINING THE CLINICAL STAGE

Staging of NSCLC involves multiple modalities; guidelines recommend use of combined positron emission tomography (PET) and computed tomography (CT) if available, and otherwise a CT scan alone. In case of suspicious mediastinal nodes on the scan, meaning nodes with fluorodeoxyglucose (FDG) uptake or with a small axis diameter >1 cm, minimally invasive techniques are recommended to obtain a tissue diagnosis of these nodes.[4,20] Techniques used include endoscopic ultrasound (EUS) or endobronchial ultrasound (EBUS). If these tests prove to be negative, a (video) mediastinoscopy is recommended. In patients with an intermediate risk of mediastinal lymph node metastasis, meaning a tumor >3 cm (dependent on which guideline is followed),[20,21] a central tumor or a tumor with suspicious N1 lymph nodes, invasive staging of the mediastinum is also recommended, starting with EUS/EBUS. If results are negative but suspicion is high a (video) mediastinoscopy is recommended as well. Magnetic resonance imaging (MRI) of the brain is recommended in patients with stage III disease.[4,21] Accuracy of clinical staging decreases in higher stages of NSCLC.[8] See Figure 1 for the staging algorithm used in most guidelines.

For this article the 7th edition of the TNM system is used, since most literature references used in this review refer to this edition.[22] Inaccuracy in staging is caused by a shift from a clinical stage to a different pathological stage. For example, a patient can shift to a pathological higher T-stage if the tumor size is bigger than expected, if there was unexpected infiltration of the visceral pleura or if unexpected, separate tumor nodules are found in the resected specimen. A higher pathological nodal stage can be caused by unforeseen N2 disease. On the other hand, downstaging, especially of T-stage is also possible, for example because of an inflated lung when scanning, inflammation, infiltration or edema.[23] Currently the

TNM 8th edition has been introduced in several countries and is due to be implemented in the United States in 2018. Most important changes in the new TNM are: a separate T-stage for every centimeter in growth up to 5 cm, change of tumors from 5–7 cm to T3 stage instead of T2, ingrowth in diaphragm moves to T4 stage instead of T3. An extra category, M1c, was added to stage patients with multiple metastases in one or more organs outside the thorax.[24] In the future this detailed subdivision, especially in T-stage, may lead to more inaccuracy between cTNM and pTNM.
To present the evidence on clinical staging and the implications on adjuvant chemotherapy we will give an overview of the literature for three different clinical stages:
1: Patients with clinical stage I disease
2: Patients with clinical stage II disease
3: Patients with clinical stage III disease (especially stage IIIA-N2)

## CLINICAL STAGE I PATIENTS

### Staging

Patients with clinical stage I disease have a tumor ranging from 0–5 cm and no hilar or mediastinal lymph node involvement. Depending on which guideline is used, staging of the mediastinum is indicated in tumors 3–5 cm.[20,21] Clinical staging is fairly accurate, ranging from 65–75% accuracy between cTNM and pTNM in the era before PET-CT.[6,12–14] Recently the Dutch Lung Surgery Audit (DLSA), a nationwide clinical audit in the Netherlands, was used to examine how accurate clinical staging of stage I tumors was done in 2013 and 2014 in the Netherlands.[9] Accuracy between cTNM and pTNM was 59.9% in a population of 1,555 patients, who all had a PET-CT scan in their work up. Combining the subgroups of stage Ia and stage Ib together showed an accuracy of 76.6% for all stage I patients. Of all patients, 22.6% were upstaged to a pathological stage II or higher, which is an indication for adjuvant chemotherapy. Especially patients with larger tumors from 3–5 cm (T2a) had a high risk of having lymph node metastasis (21.2%). The number of unforeseen N2 nodes in cT2a patients was as high as 6.7%. These data support the guideline of the European Society of Thoracic Surgeons (ESTS), which advices mediastinal staging in patients with tumors >3 cm.[20] This is based on a lower negative predictive value (NPV) for PET-CT in patients with a tumor >3 cm, which has been proven in various studies, especially in patients with adenocarcinoma.[25,26]

**Primary treatment**

For a patient with a clinical stage I tumor who is fit for surgery, two primary treatment options are available:

- Surgical resection, with adjuvant chemotherapy if the pathological stage after resection is stage II or higher
- SABR, with or without adjuvant chemotherapy

It is difficult to state which treatment option is best in patients with stage I NSCLC: three stage III randomized controlled trials were initiated to compare SABR to surgery for resectable stage I NSCLC, but all were closed prematurely due to poor accrual: the STARS trial [ClinicalTrials.gov identifier: NCT00840749], the ROSEL trial [NCT00687986], and the ACOSOG Z4099 trial [NCT01336894]. In 2015, the only randomized evidence, a pooled analysis of the limited included patients in the STARS and ROSEL trial, was published. In this analysis survival and locoregional recurrence were comparable between SABR and surgical resection.[27] Many researchers commented on this study stating it was highly underpowered (2.8% out of a total of 2410 intended patients was included).[28] At present we should still consider surgical resection as the gold standard treatment. However, SABR is a good alternative with good outcome and additional randomized trials will analyze SABR in comparison with surgery, to analyze what therapy is best in patients fit for surgery but also suitable for SABR.

**Adjuvant therapy**

If a patient receives a surgical resection for a clinical stage I tumor, 5-year survival in the pre video-assisted thoracoscopic surgery (VATS)-era was between 60–80%.[15,16] If a patient has a pathological stage II or higher after surgical resection, adjuvant chemotherapy is indicated. This increases survival with 4% in 5 years according to the Cochrane review on adjuvant chemotherapy in curatively resected NSCLC.[18] It is difficult to present data on the survival of a patient receiving SABR and adjuvant chemotherapy, hardly any trials have been published on this subject. Louie and colleagues published a review in 2014 in which this problem is addressed.[29] They describe that models have been developed to predict systemic disease, and it is proposed that patients with larger tumor size, higher pretreatment FDG-PET maximum standard uptake value (SUV-max), as well as contact with mediastinal pleura, might be offered adjuvant chemotherapy after SABR to prevent disease recurrence. Unfortunately there are no data that describe

the survival of patients with this treatment strategy. Because of the lack of data on this subject close follow up of patients after SABR is recommended. After radical resection of stage I disease, postoperative radiotherapy (PORT) is not indicated, since this has no added benefit.[30,31] In patients with resected stage I disease and a positive resection margin (R1) postoperative radiation therapy is advised.[16] Figure 2 shows the different treatment options in clinical stage I patients and the respective survival rates.

## CLINICAL STAGE II DISEASE

### Staging

Clinical stage IIA disease is comprised of T2bN0 or T1a-2aN1 disease. Clinical stage IIB disease consists of T2bN1 or T3N0 disease.[22] Clinical staging in these patients is moderately accurate. This is mostly due to the necessity of staging the mediastinum. Guidelines by the ESTS and American College of Chest Physicians (ACCP) recommend staging the mediastinum in patients with an intermediate risk of mediastinal lymph node metastasis: hence this is advised when a patient has suspicious N1 lymph nodes on PET-CT, a central tumor or a tumor >3 cm (see Figure 1).[4,20] The rationale for this advice is a study that showed that patients with N1 disease on a CT scan have N2 or N3 nodes in 30%.[32] The evidence for mediastinal staging in central tumors comes from a study that showed the number of patients with unforeseen N2 disease in central tumors was almost 10 times higher than in peripheral tumors (2.9% *versus* 21.6%).[11] Advice on how to stage the mediastinum is largely based on the ASTER trial. This trial showed a sensitivity of 79% for surgical staging of the mediastinum alone, 85% sensitivity for endosonography alone and 94% sensitivity for endosonography followed by surgical staging.[33] It is therefore that the staging algorithm starts with EUS combined with EBUS, and when these prove negative it should be followed by mediastinoscopy. This approach results in fewer unnecessary thoracotomies. EBUS can be used to visualize and biopsy mediastinal stations 2R/2L, 4R/4L, 7 and hilar stations 10, 11 and 12. EUS is particularly useful for mediastinal stations 4L, 7, 8, 9 and the left adrenal. Mediastinoscopy can be used to biopsy stations 2R/L, 4R/L and 7. Where the ASTER trial started with staging the mediastinum endosonographically with EUS, in a study by Kang and colleagues it was proven that adding EBUS to EUS increases the accuracy and sensitivity of mediastinal staging significantly. It is therefore concluded that EBUS is the

primary procedure and an EBUS centered approach should be chosen to stage the mediastinum, followed by EUS.[34]
If needed, more radical lymph node dissections are possible by video-assisted mediastinoscopic lymphadenectomy (VAMLA) or transcervical extended mediastinal lymphadenectomy (TEMLA). Although the published series come from dedicated centers the NPV can reach 100% and sensitivity 100%.[35,36] However data on these techniques and diffusion into clinical practice are very limited and the increase in staging accuracy comes with the cost of a higher morbidity than in (video)mediastinoscopy.
Table 1 shows the median sensitivity and specificity of the different mediastinal staging techniques according to the ACCP clinical practice guidelines.[4] Although median sensitivity and specificity of these separate diagnostic tests are high, an analysis on stage I–IIIB tumors showed an accuracy of 54.6% between cTNM and pTNM in the Netherlands, in a population of 2,336 patients in 2013 and 2014 who all had a PET-CT.[8] As can be seen in Figure 3 57% of clinical stage II patients had pathological stage II disease in this dataset, 24% is downgraded to pathological stage I disease and 19% is upgraded to pathological stage III disease. In this series with 6.3% unforeseen N2 nodes especially clinical staging of nodes proved to be difficult. Table 2 shows all studies comparing cTNM and pTNM and their respective accuracies, which range from 47–91%. The study from Jakobsen and colleagues is a positive outlier; they used a different definition for discrepancy, since it had to have therapeutic consequences for the patient and SABR and induction therapy were not used as primary treatment options.[10]

**Primary treatment and adjuvant treatment**

In patients with clinical stage II disease the current opinion is that when a patient is fit for surgery a radical resection is advised. Dependent on the pathological outcome adjuvant therapy is given. If a patient has pathological stage I disease there is no indication for adjuvant therapy. If a patient has pathological stage II disease, adjuvant chemotherapy is advised, as described earlier. As mentioned before this gives a 4% benefit in 5-year survival according to the Cochrane review on patients who get a resection with curative intent.[18] In a randomized controlled trial (NATCH trial) that allocated patients to adjuvant chemotherapy before their surgery it was shown that not all patients (33.8%) actually started the planned treatment after resection, due to patient refusal, surgical complications or physicians

recommendation.[19] Even if the start of adjuvant chemotherapy is delayed due to slow recovery after surgery it remains effective if started up to 4 months after surgery.[37,38]

If a patient is resected and unforeseen N2 nodes are found (pathological stage IIIA-N2) in the resected specimen it is advised to give adjuvant chemotherapy. The goal of this treatment is to reduce risk of relapse based on micrometastasis.[39] Adjuvant radiotherapy is not the standard treatment in these patients; the value of this treatment is under research in the LungART trial.[40] In a large retrospective cohort from the Netherlands the 4-year survival for upfront surgery is 39% for patients with unforeseen N2 disease.[41]

After radical resection of stage II disease, there is no place for PORT, since this has no added benefit on survival.[30,31] However, in patients with resected stage II disease and a positive resection margin (R1) postoperative radiation therapy is advised.[16]

## CLINICAL STAGE III DISEASE

### Staging

Clinical stage III disease is comprised of a varied group of patients for whom different treatment options are available. Clinical stage IIIA consists of patients with T1a-2bN2, T3N1-2 or T4N0-1 disease. Clinical stage IIIB disease is T4N2 or any N3 disease.[22] Correct clinical staging in these groups is difficult, and it is known that accuracy of clinical staging decreases in higher stages. The staging algorithm is the same as for other NSCLC patients described earlier in this article, and a MRI of the brain is advised in clinical stage III disease to rule out metastasis. In all patients with clinical stage III invasive mediastinal staging is indicated, either because of a tumor >3 cm, a central tumor with extension in mediastinal structures, N1 nodes or suspicious N2 nodes on the PET-CT.[4,20,39] Especially patients with suspicious N2 nodes deserve extra attention: false positive PET findings can cause incorrect upstaging, tissue confirmation is therefore always mandatory to prevent denying a curative resection.[42,43] Accuracy of clinical staging in stage III patients is around 51% in a study comparing staging and treatment in stage III patients with an upfront resection in the Netherlands.[41] If a patient is treated with induction therapy, restaging the mediastinum is difficult: CT and PET are unreliable and a repeat mediastinoscopy can be technically difficult. EBUS can reach a sensitivity of 64-76%.[36,44] There is no preferential

restaging technique; it depends mainly on the invasive method used initially to stage the mediastinum.[45] It is very important to identify the subcategories correctly in stage III disease, because treatment differs substantially between them.[39] Before any treatment is started a multidisciplinary team (MDT) should classify a patient in one of three groups:
- Potentially resectable
- Potentially resectable with an increased risk of incomplete resection
- Definitely unresectable

**Primary treatment and adjuvant treatment**

Patients with potentially resectable disease who have histologically or cytologically proven clinical stage IIIA-N2 disease are advised to be treated by induction therapy with chemo(radio)therapy followed by resection or definitive chemoradiotherapy. The North American Intergroup trial is the only randomized trial that investigated treatment with full-dose definitive concurrent chemoradiotherapy *versus* induction-concurrent chemotherapy and radiotherapy followed by surgery; both groups were equal in survival although progression-free survival was better in the group that also had a resection. It is advised though that a patient should be able to have a lobectomy after induction therapy, since mortality after pneumonectomy is unacceptably high (26% 30-day mortality rate in right sided pneumonectomies). Cisplatin and etoposide were used as chemotherapeutic agents in this trial.[46] A manuscript describing an analysis, systematic review and meta-analysis showed a much more acceptable rate of 7% 30-day mortality in patients with a pneumonectomy after neoadjuvant therapy though, with a significant higher mortality in right sided pneumonectomies compared with left sided pneumonectomies (11% *versus* 5% respectively).[47]
In a retrospective analysis of the Dutch Cancer Registry by Dickhoff and colleagues, overall survival in 4 years was 51% with induction therapy and resection. This analysis consisted of a heterogeneous group of stage IIIA patients combining results of stage IIIA-N2 patients and patients with T4 disease.[41]
In patients with potentially resectable disease with an increased risk of incomplete resection it is advised to give concurrent chemoradiotherapy as induction therapy followed by surgery. This is a strategy that can be used for sulcus superior tumors as well as for central T3/4 tumors. Cisplatin and etoposide are used for this purpose again.[48] Eberhardt and colleagues

confirmed these findings in the ESPATUE trial, in which patients with pathologically-proven stage IIIA-N2 disease or selected stage IIIB patients received induction chemotherapy, as well as concurrent chemoradiotherapy (with cisplatin, paclitaxel and vinorelbine). After this, patients were restaged and when the tumor was resectable they were randomized between either a chemoradiotherapy boost or surgery. For both arms overall survival was good (40% *versus* 44%), just as progression-free survival (35% *versus* 32%).[49] Patients with pathologically-proven and unresectable N2 disease were randomized in the EORTC trial; induction therapy with three cycles of chemotherapy was given and patients who showed any response were randomized to two arms. The first arm was given surgical resection; the second arm was given radiotherapy. No difference in overall survival or progression-free survival was noted (16.4 *versus* 17.5 months).[50] Hence in unresectable disease, it is not advised to do a resection after induction therapy. Definitive radiotherapy and chemotherapy combinations remain the treatment of choice for these patients. Concurrent chemoradiotherapy gives better overall survival rates than sequential chemoradiotherapy.[51] Figure 4 shows the different treatment options in clinical stage III patients and the respective survival rates. It is suggested PORT might give a survival benefit in patients with unforeseen N2 disease, this is still under research in the LungART trial.[40] In patients with positive bronchial margin (R1) after resection who were not treated with radiotherapy preoperatively this should be considered.[16]



## CONCLUSION

This article describes how accurate clinical staging is for different clinical stages and what consequences this has for treatment and especially adjuvant chemotherapy. Although separate diagnostic modalities in staging lung cancer have fair sensitivities and specificities, all modalities combined have moderate accuracy in diagnosing the correct stage NSCLC of a patient. As we tried to show in this article, staging algorithms differ per stage, just as treatment options. Surgical resection often changes the clinical stage to a different pathological stage. Because of this change the choice of adjuvant treatment should always depend on the pathological stage if available. Since accuracy of staging is low, it is important to obtain tissue confirmation before denying a potentially curative resection. Because of this complexity we advise that every patient with NSCLC is discussed in an

MDT after every new investigation or surgery. After assessment of the actual disease stage it should be determined whether additional investigations are warranted, and whether current evidence indicates adjuvant treatment at that moment. Future research on clinical staging of NSCLC should focus on ways to improve the accuracy of the staging process and the reproducibility of the outcomes and functioning of the MDT.

In clinical stage I patients, surgical resection or SABR are the modalities of choice. As we showed there is no evidence for adjuvant chemotherapy in patients treated with SABR, especially because the pathological stage remains unknown in these patients and it is assumed they have pathological stage I disease. In patients with clinical stage II disease surgery is the treatment of choice: after resection the pathological stage is known and adjuvant treatment can be chosen. In patients who had a radical resection adjuvant chemotherapy gives a 4% survival benefit when the pathological stage is stage II or higher. In patients with pathological stage III disease the overall survival is improved with adjuvant chemotherapy, but this will only lead to an overall survival of 39% in 4 years. When a patient is suspected of clinical stage III disease it is mandatory to confirm N2 disease by tissue biopsies of the mediastinal lymph nodes. This alters the primary choice of treatment and it should be decided if a radical resection would be possible. If this might be an option, advice is to give induction therapy and do a resection after restaging. With this strategy 5-year survival can reach 44%. If a patient is definitely unresectable chemoradiotherapy is the treatment of choice. In all chemotherapy regimens cisplatin plays a role. Postoperative radiotherapy is mainly reserved for patients with R1-resections.

**TABLE 1.** Median sensitivity and specificity of invasive diagnostic modalities to stage the mediastinum according to the ACCP clinical practice guidelines.[4]

| Modality | Sensitivity | Specificity |
|---|---|---|
| Mediastinoscopy | 78% | 100% |
| Videomediastinoscopy | 89% | 100% |
| EBUS | 89% | 100% |
| EUS | 89% | 100% |
| Combination EUS/EBUS | 91% | 100% |

ACCP = American College of Chest Physicians
EBUS = endobronchial ultrasound
EUS = endoscopic ultrasound

**TABLE 2.** Studies on accuracy of clinical staging comparing clinical or imaging TNM with pTNM.

| Author | Year | Version TNM | Comparison[a] | Clinical stage | Patients | Accuracy | Unforeseen N2 |
|---|---|---|---|---|---|---|---|
| Gdeedo[7] | 1997 | 1992 | iTNM vs pTNM | I-IV | 74 | 35% | |
| Cetinkaya[5] | 2002 | 1997 | cTNM vs pTNM | I-IV | 180 | 48% | |
| D'Cunha[6] | 2005 | 1997 | cTNM vs pTNM | I | 422 | 72% | 13.5% |
| Lopez-Encuentra[12] | 2005 | 1997 | cTNM vs pTNM | I-IV | 2,377 | 47% | |
| Lee[11] | 2007 | 1997 | cTNM vs pTNM | I | 224 | 75% | 7.1% |
| Macia[13] | 2009 | 1997 | cTNM vs pTNM | I-IV | 176 | 58% | 11.9% |
| Stiles[14] | 2009 | 1997 | cTNM vs pTNM | IA | 266 | 65% | 11.7% |
| Jakobsen[10] | 2013 | | cTNM vs pTNM | I-IV | 810 | 91% | |
| Heineman[8] | 2016 | 2007 | cTNM vs pTNM | I-IIIB | 2,336 | 54.6% | 6.3% |
| Heineman[9] | 2016 | 2007 | cTNM vs pTNM | I | 1,555 | 59.9% | 5.5% |

[a] iTNM = imaging TNM, cTNM = clinical TNM, pTNM = pathological TNM

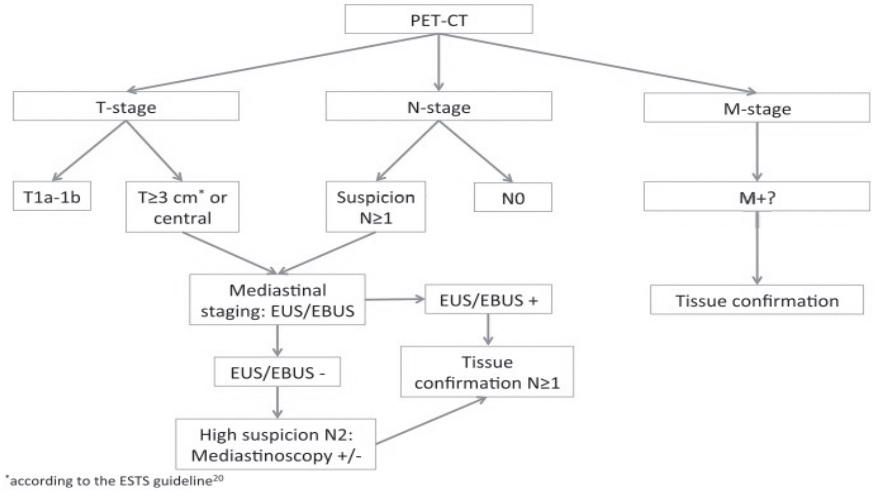



**FIGURE 1.** Staging algorithm for NSCLC.

CT = computed tomography; EBUS = endobronchial ultrasound; ESTS = European Society of Thoracic Surgeons; EUS = endoscopic ultrasound; PET = positron emission tomography; US = ultrasound



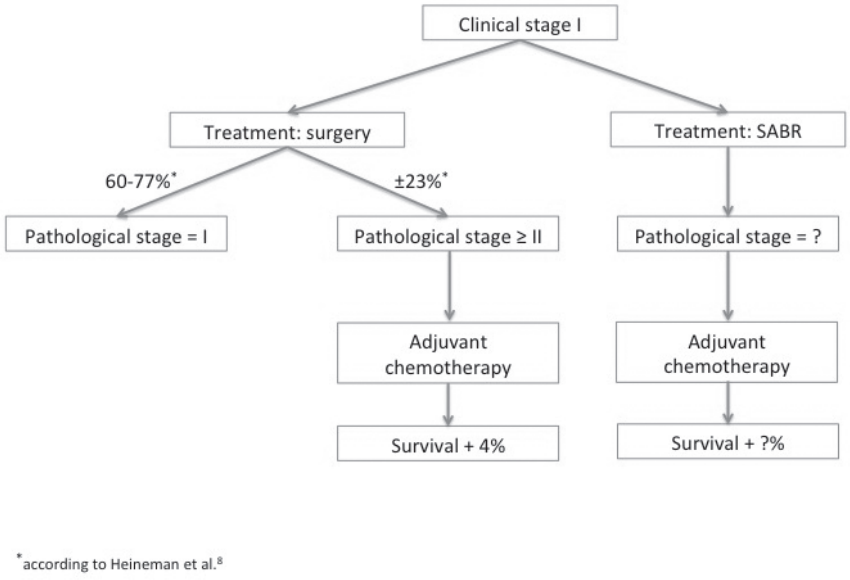
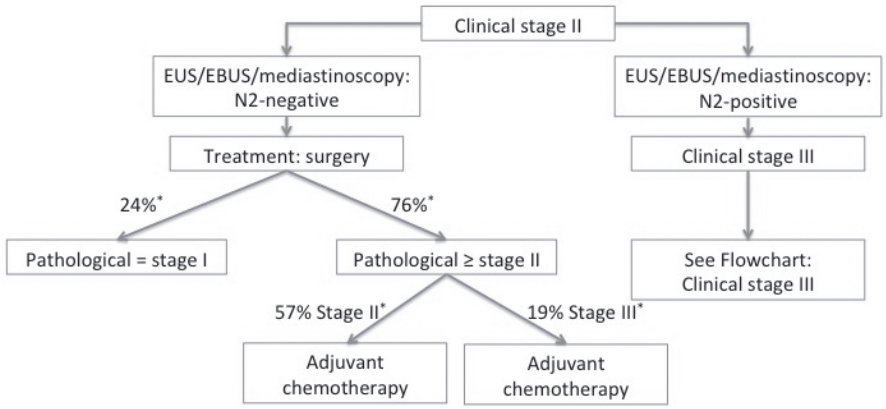



**FIGURE 2.** Flow chart stage I NSCLC

SABR = stereotactic ablative radiotherapy




*according to Heineman et al.[8]

**FIGURE 3.** Flow chart stage II NSCLC.

EBUS = endobronchial ultrasound; EUS = endoscopic ultrasound

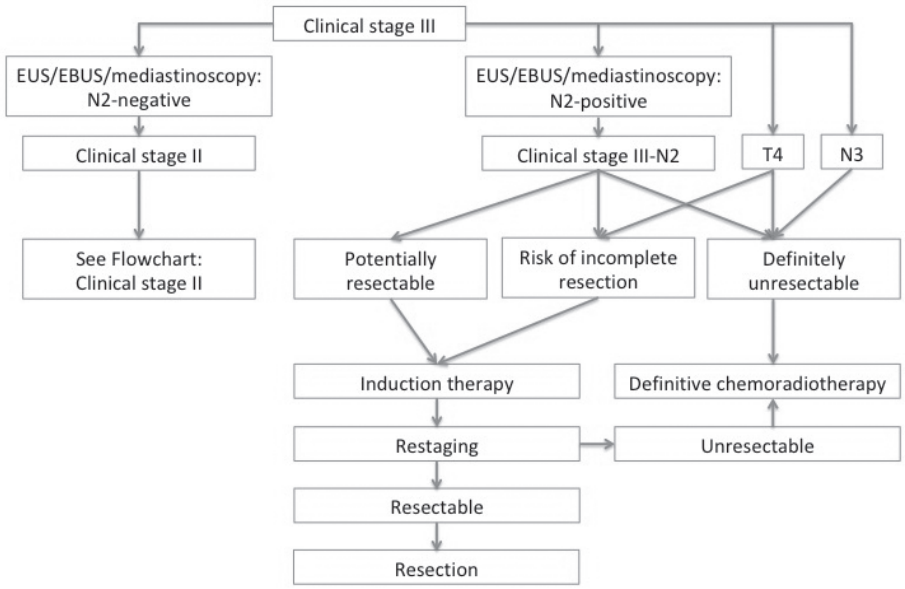



**FIGURE 4.** Flow chart stage III NSCLC.

EBUS = endobronchial ultrasound; EUS = endoscopic ultrasound

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# CLINICAL STAGING OF NSCLC: STILL ROOM FOR DEBATE

9

*J Thorac Dis. 2018;10;S2083-5.*

D. J. Heineman
J. M. A. Daniels
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It is with great interest that we took notice of the expert knowledge on staging of non-small cell lung cancer (NSCLC) and the implications on adjuvant chemotherapy expressed in the two invited editorials on our previously published article entitled "Clinical staging of NSCLC: current evidence and implications for adjuvant chemotherapy".[1] We read the reviews entitled "New classification—new problems to solve" by Dr. Zieliński and Dr. Kwiatkowski[2] and "Meet the new boss: lung cancer staging" by Dr. Begnaud and Dr. Kratzke[3] and would like to respond to the issues that have been raised.

Both editorials point out the use of the 7th edition of the TNM instead of the new 8th edition of the TNM, which was introduced in 2016.[4] In our review we have deliberately chosen the 7th edition of the TNM because this has been used from 2009 until 2016 and most recent literature on staging NSCLC uses this 7th edition. The 8th edition has been introduced in 2016 but its use has not been implemented worldwide yet. It is not possible to describe the impact of clinical staging and implications on adjuvant chemotherapy in the new edition, when there are ample studies describing this. Dr. Zieliński and Dr. Kwiatkowski described a very interesting phenomenon and we would like to thank them for pointing this out: there is an interesting shift in tumor stage when comparing the staging systems, meaning that a tumor with a diameter >7 cm and no involvement of lymph nodes used to be T2 and stage I according to the 6th edition, T3 and stage IIB according to the 7th edition and T4 and stage IIIA according to the 8th edition. The TNM classification is largely based on survival differences between stage groups and apparently, the impact of tumor size on overall survival is increasingly gaining acknowledgement.[4]

We do not support the statement that there are no established indications for adjuvant chemotherapy in stage II (N0) patients and believe however that there are indications for adjuvant chemotherapy for patients based on pathological T stage alone, as stated in our article. The article of Howington et al. that is referred to by Dr. Zieliński and Dr. Kwiatkowski makes an important comment on a subanalysis on stage II (N0) patients in the CALGB 9633 and that they may benefit from adjuvant chemotherapy in larger N0 tumors (>5 cm).[5,6] This is supported by the more recent data from the updated American Society of Clinical Oncology (ASCO) guidelines, that states that adjuvant cisplatin-based chemotherapy is recommended in patients with completely resected stage IIA, IIB or IIIA disease.[7] Next to this there is some evidence from two trials that even supports the use of

adjuvant chemotherapy in patients with tumors smaller than 4 cm and N0 disease.[8,9] Our recommendation with a cut-off value of 5 cm (stage IIA in the 7th edition of the TNM) might even be called tentative in regard to the CALGB 9633 subanalysis, that recommends adjuvant chemotherapy in patients with a tumor >4 cm (which is still stage IB in the 7th edition of the TNM).6 In this respect Dr. Begnaud and Dr. Kratzke are right in stating that the cut-off should be 4 cm, although they also righteously state that this is based on a post hoc retrospective analysis of these data. We agree that the option of adjuvant chemotherapy should be considered in patients with a resected stage IB tumor (in the 7th edition of the TNM) that is larger than 4 cm. In the new edition of the TNM this will be more clear since stage IIA tumors are >4 cm in the 8th edition of the TNM.[4]

Another difficult issue that all reviewers point out is what to do with locally advanced NSCLC, especially restaging after induction therapy. Accuracy of staging seems to decrease in higher stages, where correct staging is of vital importance. Therefore, mediastinal N2 node involvement should always be cytologically or histologically proven before induction therapy can be initiated, especially since Positron emission tomography-computed tomography (PET-CT) has a tendency to over-estimate mediastinal involvement.[10] Restaging after induction therapy poses an even more difficult task, since accuracy of diagnostic modalities decreases after induction therapy. We do agree with Dr. Zieliński and Dr. Kwiatkowski's statement that one should make a subdivision between yN0-1 and yN2 disease. The first group should be treated with surgery after induction therapy since there is a prognostic benefit. In the last group, it is unclear if additional surgery after induction therapy improves survival.[11,12]

In conclusion, lung cancer staging remains a controversial topic and a new edition of the TNM poses additional challenges. Facing so many challenges in the staging and treatment of lung cancer, there is certainly no time for nihilism. Instead, we should be optimistic and make a global ongoing effort to improve the outcome for lung cancer patients. An open scientific debate is the way forward and therefore the critical appraisal of our work by the reviewers is greatly appreciated.





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# 10 DISCUSSION AND FUTURE PERSPECTIVES

This thesis describes the staging of patients with non-small cell lung cancer (NSCLC) in daily clinical practice. Clinical staging of NSCLC is not optimal at present in the Netherlands, with a concordance between clinical stage (cTNM) and pathological stage (pTNM) in just over 50% of the cases. Accuracy of clinical staging in the literature shows a wide range of 35-91%, with higher accuracy reported for earlier stage disease.[1-7] The Danish group reported an accuracy of 91%,[1] but used a different definition for discordance: a difference in cTNM and pTNM, but restricted this to those patients in whom the discordance would have had clinical consequences, e.g. a change in primary treatment (cT1-3 to pT4 and cN0-1 to pN2-3 or cN2 to pN3). Such a strategy is however based on the assumption that patients with a resectable tumor are only amenable for surgery. However, in modern lung cancer treatment, additional modalities such as radiotherapy and/or chemotherapy are often combined with surgery in a neo-adjuvant or adjuvant setting (depending on the exact stage) for optimal results.[8] This underlines the vital importance of accurate staging. Further improvements in the quality of patient care require a greater awareness among doctors of the importance of correct initial staging. In addition, Multidisciplinary Tumor Boards (MTB's) should have an important role in the monitoring and reinforcement of guideline adherence and quality control of all diagnostic modalities.

Correct staging in stage I patients is important, especially because of the emerging role of SABR as an alternative to the gold standard of surgical resection. Previously prospective randomized trials of stereotactic ablative radiotherapy (SABR) versus surgical resection lacked power due to insufficient accrual.[9] While awaiting the results of additional randomized trials, it is important to acknowledge the fact that lymph node dissection is lacking in patients who are treated with SABR. Clinicians should be aware that the chance of unforeseen N1 or N2 disease increases with certain tumor characteristics (e.g. tumor diameter, central location). In such cases with a higher a priori chance of lymph node involvement, we advise accurate staging and surgical resection with systematic lymph node dissection or, if radiotherapy is the preferred modality, invasive mediastinal staging of hilar and/or mediastinal lymph node metastases before the start of the treatment. The mediastinal staging guideline of the European Society of Thoracic Surgeons recommends mediastinal staging in tumors >3 cm, we recommend compliance with this guidelines especially when a non-surgical treatment is considered.[10-13] However, when considering the clinical consequences of omitting mediastinal staging, Louie and colleagues have suggested that

when assuming a 15% occult nodal metastasis rate and an estimation of only 66% of eligible patients finally receiving adjuvant chemotherapy, only 0.5 lives are prolonged for every 100 patients undergoing mediastinal staging.[14]

Locally advanced NSCLC is more difficult to stage correctly than early stage NSCLC, but correct staging can have a survival benefit for patients. It is important to distinguish resectable stage III disease from irresectable stage III disease before start of treatment. According to current guidelines, resectable stage IIIA-N2 disease could be treated with induction therapy followed by resection, instead of upfront resection combined with adjuvant therapy (4-year survival 51% versus 39% in the Netherlands, respectively).[8] However, the results of the PACIFIC trial will have significant impact in the treatment of locally advanced disease in the near future. This trial showed better survival in patients with unresectable stage III disease treated with chemoradiotherapy followed by Durvalumab, compared to chemoradiotherapy followed by placebo, which used to be the treatment standard (24 month survival of 66.3% and 55.6% respectively, p = 0.005).[15] Immunotherapy as adjuvant therapy or neoadjuvant therapy in resectable stage III NSCLC is currently under investigation. Theoretical advantages of neoadjuvant immunotherapy instead of adjuvant immunotherapy are multiple, such as an earlier treatment of micrometastases, in vivo assessment of treatment response and thus a better selection of patients that will benefit from surgical resection.[16] The SEISMIC trial will investigate the role of comprehensive mediastinal staging using EUS in addition to EBUS, in patients with irresectable locally advanced NSCLC with clinical N2/N3 disease that are planned for radical (chemo)radiotherapy.[17]



When considering invasive diagnostic modalities, the role of (video) mediastinoscopy in clinical staging of NSCLC is currently the subject of debate, as its quality is related to the extent of node sampling and surgeons' experience.[18-20] The exact role of (video)mediastinoscopy in the era of Positron Emission Tomography–Computed Tomography (PET-CT), endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) is currently under investigation in the prospective, randomized MEDIASTrial.[21] It is plausible that results of this trial may reveal that (video)mediastinoscopy can be omitted, as long as EBUS/EUS are performed with high sensitivity and specificity. In daily clinical practice, only 51% of (video)mediastinoscopies is technically performed according to the Dutch guideline [Chapter 6]. If a

(video)mediastinoscopy is performed in the work-up of NSCLC, we advise to adhere to the Dutch guideline, instead of the less stringent European guideline: this will lead to significantly less unforeseen N2 nodes (8.6% versus 11.9%, p = 0.043) [Chapter 6].

Outcomes of national audits should be synchronized between different countries in order to compare different countries, healthcare systems and types of governance. This will also enable assessment of effects on clinically relevant outcomes after introduction of a policy such as centralization of lung cancer surgery. At present, it is difficult to draw firm conclusions about differences in staging between Denmark and the Netherlands, based on the national registries. The ESTS database is an example of a database that covers hospitals from multiple countries within one dataset, in which the data definitions are very well described.[22,23] Unfortunately, in this database it remains unclear whether participating hospitals register all consecutive lung surgery patients or a selection, and if there are hospitals in the participating countries that perform lung surgery but do not register patients at all. The role of voluntary registration is important: the Society of Thoracic Surgeons General Thoracic Surgery Database in the United States recently reported that hospitals participating in the database have shorter postoperative length of stay and lower mortality than non-participating hospitals in patients that undergo a lobectomy.[24] In order to improve the quality of lung cancer surgery at an international level, it is crucial to synchronize and link the national lung cancer surgery registries.

**Limitations in all studies**

The use of data from the DLCA has certain limitations: data is self-reported by clinicians or trained personnel, so bias could be introduced. In order to prevent bias, data is verified by an external organization and compared with the Netherlands Cancer Registry to increase reliability. Secondly, the published studies in this thesis reflect data collected in its early period, when survival data were unavailable as the registration was performed for less than 5 years. Consequently, we missed the opportunity to show survival data related to under- or overstaging patients. Thirdly, in the early studies, some essential details were lacking in the database, for example position of the tumor (central or peripheral). This is essential information for analyzing guideline adherence regarding mediastinal lymph node staging. However, some of these missing variables in the early studies have been added to

the audit because of the results of this thesis. Fourth, the gold standard, the pTNM, is a standard that can be debated. The quality of the pTNM is very much dependent on quality of the surgery, but also dependent on the quality of the pathologist. The accuracy of the lymph node dissection is not recorded in the audit: participants only register what lymph node stations were biopsied or dissected, but not how many nodes were harvested and if dissection or sampling was performed. For example, we demonstrated that lymph node station 7 is dissected or sampled in only 73.9% of patients, even if this station should be dissected in every patient according to current guidelines, regardless the tumor location.[25] This concern has been highlighted recently in patients with sublobar resections, where lymph node harvest was proven to be inaccurate, especially in patients that received a non-anatomical wedge resection. Not only does this influence the reliability of the pTNM, even more importantly it influences the oncological outcome of patients.[26] Furthermore, the DLCA does not record how decisions are made in the MTB's, making it impossible to know if a team deliberately ignored the guidelines due to certain patient characteristics. The last limitation we encountered in the study comparing Denmark and the Netherlands was the difference in data definitions between the two datasets, which precludes firm conclusions impossible as outlined in the previous paragraph.

**Future perspectives**

Tumor biology is now recognized as a crucial factor in clinical decision making for stage III and IV NSCLC (e.g. histological subtype, mutational status, PD-L1 status). However, we expect that tumor biology will assume an equally important position in the management of patients with early stage lung cancer in the near future. Despite curative intent treatment, 60% of appropriately treated patients still develop tumor recurrence. Since adjuvant immunotherapy has led to improved survivals in patients with unresectable stage III disease treated with concurrent chemoradiotherapy,survival in early stage NSCLC might be improved as well, and studies are ongoing.[15, 27-33] Correct clinical staging in these trials is of the utmost importance: if clinical staging is unreliable, it will remain unknown what actual stage (and corresponding prognosis) patients had when induction therapy is given with e.g. immunotherapy, chemotherapy or both. For example, if a patient with small nodal metastasis that are occult receives induction therapy and these metastasis resolve, the pathological stage post-resection will not reveal

the initial, unfavorable, prognosis of this patient and the higher chances of disease recurrence.[34]

Shared decision making will play an even more important role in the near future. In shared decision making, clinicians should provide the patient with information about all the different options, after which the patient choses their preferred treatment based on their values. However, it is difficult for treating physicians to synthesize the available information in the context for a specific patient, and it is difficult for a clinician that their own values interfere as well in advising the patient.[35] This will play an important role not only for patients and clinicians, but also for study designs: the SABRTOOTH study, a study comparing SABR versus surgery in high risk patients with stage I NSCLC, showed difficulties in accrual due to patient preferences. Patients preferred SABR in this study instead of surgery, making it not feasible to conduct a large randomized controlled trial in the United Kingdom.[36]

More interesting results will be available in the near future. Many interesting trials are currently including patients to answer a wide variety of clinical questions. For example, for stage I disease several randomized trails on SABR versus minimally invasive (sub)lobar resections are recruiting.[37-40] This is an important topic, especially for older patients and patients with comorbidities. Surgical techniques are also evolving, with uniportal Video-Assisted Thoracic Surgery and Robot-Assisted Thoracic Surgery as main examples. This enables surgeons to perform more complex operations with less pain and faster recovery. With these perspectives, diagnostic procedures to diagnose and stage lung cancer will have to be as accurate as possible, so patients can be offered a tailor-made treatment. The role and the quality of the MTB will become more and more important with these multidisciplinary diagnostic and therapeutic options.

**Future research perspectives**

For research in the area of lung cancer staging, it is crucial to understand the impact of correct staging on patient survival. To this end, our research group will compare survival data from correctly staged, understaged, and overstaged patients, with data from the Dutch Cancer Registry. We assume that understaged patients might have a worse prognosis since they are undertreated, and overstaged patients might have a worse prognosis because they suffer from overtreatment. If in this manner,

accuracy of staging can be directly related to survival, it will become easier to synchronize registries and implement improvement in quality of health care for lung cancer patients.
To study the variation between MTB's with regard to clinical decision making we have recently completed a study (data analysis ongoing). In this study blinded clinical data and images of ten patients with locally advanced NSCLC were discussed by different multidisciplinary tumor boards in academic and non-academic centers. Our hypothesis is that there is considerable variation in the clinical management of these patients. We believe it is important to treat patients more uniformly in every hospital in the Netherlands, to prevent differences in patient outcome. Although it seems obvious there will be differences between different lung cancer MTB's, this aspect of care has not been adequately researched previously.

**Conclusion**

In this thesis the inaccuracy between the clinical and pathological stage in patients with NSCLC in the Netherlands, is discussed. With concordance below 55% in our studies, correct clinical staging remains challenging. Clinicians should adhere to the guidelines and pursue the highest quality when performing diagnostic procedures. Without a correct clinical stage, it is impossible to make correct decisions on primary treatment in the MTB. With forthcoming studies on emerging neo-adjuvant therapies, correct clinical staging is indispensable. With these challenges ahead, multidisciplinary collaboration between surgeons, pulmonologists, radiotherapists, (nuclear) radiologists and pathologists is vital.

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# SUMMARY AND APPENDICES

II

## ENGLISH SUMMARY

This thesis describes the daily clinical practice of staging patients with non-small cell lung cancer (NSCLC). In the introduction (**Chapter 1**), the staging algorithm is described. The clinical stage for patients with NSCLC - which can be aggregated from the T (tumor), N (node) and M (metastasis) descriptors, guides the decision making process during multidisciplinary tumor board (MTB) discussions. The staging algorithm usually consists of a fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT), combined with invasive staging modalities to stage the hilar and mediastinal lymph nodes, such as an endoscopic ultrasound (EUS), endobronchial ultrasound (EBUS), and sometimes a (video)mediastinoscopy. A magnetic resonance imaging (MRI) scan of the brain is advised in clinical stage III disease.

For all studies in this thesis, data were used from the Dutch Lung Cancer Audit (DLCA), previously known as the Dutch Lung Surgery Audit (DLSA). **Chapter 2** describes the DLSA and DLCA, explains the intention for which it was designed and how it is developed. It shows that basic patient characteristics do not differ significantly from 2012 to 2015, so selection bias does not seem to play a large role in studies from the early years of the audit. Parallel with the increased patient registration by individual caregivers and hospitals, it is interesting to note that the outcome of certain process indicators also increased significantly over the years. We believe that the audit played an important role in the increased awareness of the dutch surgeons and instigated these improvements.

The agreement of cTNM and the 'true' stage (pathological stage or pTNM) is a measure of staging accuracy and is considered an important indicator of the diagnostic process. In **Chapter 3** we analyse the accuracy between cTNM and pTNM in patients with stage IA to IIIB NSCLC who have undergone a resection with data from the DLCA (2013-2014). Of the 2,336 patients with resected NSCLC that were included in this period, 54.6% had a cTNM that corresponded with the pTNM. In this population, 15.1% of patients were clinically overstaged and 30.3% clinically understaged. Unforeseen N2 disease was found in 6.3% of patients.

In **Chapter 4** we perform an in-depth analysis of the patients with stage I NSCLC that were included in the study population described in chapter 3.

In this cohort we found a concordance between cTNM and pTNM of 59.9%, resulting in incorrect staging in 40.1% of patients. In 22.6% of patients, pathological examination of the resected specimen revealed stage II disease or higher, an indication for adjuvant chemotherapy. The other patients that were staged incorrectly moved from stage IA to IB or vice-versa. Upstaging to pathological stage II was due to nodal metastases in 14.9% (pN1-2), of which 5.5% was unforeseen N2 disease. In patients with clinical stage T2a tumors, 21.3% had nodal metastases, 14.5% being N1 and 6.7% being N2 disease.

In **Chapter 5** we describe the staging process for all patients with pathological stage IIIA disease operated from 2013 to 2015. In this study, 527 patients with pathological stage IIIA NSCLC were included, of which 254 patients had unforeseen N2 disease (7.1%). In these 254 patients, 18 endoscopic ultrasounds, 62 endobronchial ultrasounds and 67 (video)mediastinoscopies were performed preoperatively. Only a very small group of patients (n=8) with suspicious N2 nodes on the PET did not receive invasive mediastinal staging procedures. Guidelines advise neo-adjuvant therapy in patients with resectable NSCLC with limited N2 disease, however, 40 patients in this cohort were operated upfront. Unfortunately, the DLCA does not contain information on the decision-making process in these patients.

In **Chapter 6** we analyzed 1,729 patients who underwent surgery between 2012-2016 and had a (video)mediastinoscopy as part of their staging process. Primary question in this analysis was whether (video)mediastinoscopies were performed according to current guidelines, and whether the incidence of unforeseen N2 disease correlated with adherence to the Dutch or European guideline. The Dutch guideline recommends mediastinal biopsies of two ipsilateral stations, 1 contralateral station and station 7. The European guideline recommends to biopsy station 4 on the left and right side, and station 7. In 51% of patients the Dutch guideline was followed, 75% of patients were staged according to the European guideline. In patients who had a (video)mediastinoscopy that met the Dutch guideline, significantly less unforeseen N2 disease was seen compared to those meeting the European guideline (8.6% versus 11.9%, p=0.043).

In **Chapter 7** we continue with a comparison of patients from 2013 to 2016 from the Dutch and Danish national databases on lung surgical care with an

emphasis on morbidity, mortality and clinical staging. Where Danish lung surgery is highly centralized (4 centers performing lung surgery), this is not the case in the Netherlands (43 centers performing lung surgery in 2016). In addition, both countries have a different governance and financial coverage of their health care system. When focusing on patients with NSCLC without metastases, with no previous thoracic operation and no neo-adjuvant therapy, 30-day mortality was comparable between the two countries (1.5% in Denmark and 1.9% in the Netherlands (not significant), risk adjusted mortality rate 1.7% and 1.8%, respectively (not significant)). The percentage of patients with a complicated course was 24.4% and 34.8% in Denmark and the Netherlands respectively ($p<0.05$). Overall accuracy of the clinical staging process was 53.0% in Denmark and 52.9% in the Netherlands. We believe that national audits should be comparable between different countries, as this makes a comparison between different healthcare systems, governance, centralization, and their effects on outcomes possible. Unfortunately it is hard to draw firm conclusions between Denmark and the Netherlands when comparing the Danish Lung Cancer Registry (DLCR) and DLCA due to different data definitions.

**Chapter 8** comprises a review of the literature and our reflections on clinical staging, and possible implications for adjuvant chemotherapy. It is clear that in stage I NSCLC, staging is most accurate when compared with higher stages. When considering stereotactic ablative radiotherapy (SABR) as a treatment for potentially operable patients with stage I disease, it is important to take several issues into account. For example: in patients with hilar lymph node metastasis (N1) surgical resection is the primary choice of treatment, followed by adjuvant chemotherapy, which results in an increased prognosis by 4% in 5 years. When 22.6% of patients with clinical stage I is upstaged to stage II or higher after resection, adjuvant chemotherapy would be withhold in nearly a quarter of patients treated with SABR for this stage disease. Clinical stage II disease necessitates mediastinal lymph node staging, due to either tumor size, N1 lymph nodes or central localization of the tumor. An EBUS centered approach on staging the mediastinum should be chosen. Surgery remains the primary treatment modality and platinum-based adjuvant chemotherapy gives a 4% 5-year survival benefit. Stage III disease comprises a heterogeneous group of tumors, varying from small tumors with bulky, multilevel mediastinal lymph node involvement to large tumors, or tumors involving other structures such as vertebrae or major

vessels. In this patient category occult distant metastases are anticipated, so an MRI of the brain is advised in addition to the regular staging routine with at least PET and CT. Depending on resectability of the disease, curative intent treatment might be induction therapy with surgical resection or definitive chemoradiotherapy, currently followed by Durvalumab.

In **Chapter 9** we comment on two expert reviews of the manuscript in chapter 8. Subject of debate is the indication for adjuvant chemotherapy based on tumor size alone. Considering the results of the CALGB 9633 trial, patients with tumors >4cm seem to benefit from adjuvant chemotherapy. The current edition of the TNM classification makes the indication for adjuvant chemotherapy clearer as stage IIA comprises tumors >4cm instead of >5cm (compared to TNM 7, where tumors >5cm were staged as IIA). Furthermore, restaging after induction therapy is discussed; in locally advanced NSCLC, the advice should be to restage mediastinal and hilar lymph nodes after induction therapy, since the added value of surgery in yN0-1 patients is more clear than in patients with persistent nodal involvement yN2.

**Chapter 10** contains the discussion and future perspectives on clinical staging of NSCLC; a topic with many interesting challenges ahead.

## NEDERLANDSE SAMENVATTING

Dit proefschrift beschrijft de dagelijkse praktijk van het stadiëren van patiënten met niet-kleincellig longkanker (NSCLC). De introductie (**Hoofdstuk 1**) beschrijft het algoritme van stadiëren van NSCLC. Het klinisch stadium van de tumor (cTNM) bestaat uit een T, N, en M stadium. Deze cTNM is bepalend voor beslissingen in het multidisciplinair overleg (MDO). Stadiëren bestaat meestal uit een fluorodeoxyglucose-positron emissie tomografie-computertomografie (FDG PET-CT), gecombineerd met invasieve manieren van stadiëren van de hilaire en mediastinale lymfeklieren, zoals de endoscopische echografie (EUS), endobronchiale echografie (EBUS), en soms een (video)mediastinoscopie. Een kernspintomografie of magneetresonantie tomografie(MRI) van het brein wordt geadviseerd bij klinische stadium III ziekte.

In alle studies van dit proefschrift wordt data uit de Dutch Lung Cancer Audit (DLCA) gebruikt, voorheen de Dutch Lung Surgery Audit (DLSA) genoemd. In **Hoofdstuk 2** worden de DLSA en DLCA nader beschouwd, wordt uitgelegd wat het doel van de database is en hoe deze is ontstaan. We laten zien dat patiëntkarakteristieken niet verschillen tussen 2012 en 2015, waardoor het niet aannemelijk is dat selectiebias een rol speelt in de studies waarbij analyses zijn verricht met data uit de eerste jaren van de audit. In de loop der jaren is zowel registratie van patiënten door zorgprofessionals en ziekenhuizen toegenomen, als ook de uitkomst van bepaalde proces-indicatoren. Wij geloven dat deze verbetering komt door toegenomen bewustzijn voor deze indicatoren door de chirurgen die de data registreren.

De overeenkomst tussen de cTNM en het "werkelijke" stadium (pathologische TNM of pTNM) is een maat voor de accuratesse van stadiëren en wordt beschouwd als een belangrijke indicator van de kwaliteit van het gehele diagnostische proces. In **Hoofdstuk 3** hebben we data geanalyseerd van patiënten in de DLCA uit 2013 en 2014, en hebben we de overeenkomst tussen de cTNM en de pTNM berekend bij geopereerde patiënten met een stadium IA-IIIB NSCLC. Van de 2.336 patiënten met gereserceerd NSCLC die geïncludeerd zijn in deze periode, had 54,6% een cTNM die overeenkwam met de pTNM. In de geïncludeerde populatie was 15,1% van de patiënten klinisch overgestadieerd, en 30,3% was klinisch ondergestadieerd (meer gevorderd pTNM dan cTNM). Unforeseen N2 ziekte werd in 6,3% van de patiënten gevonden.

In **Hoofdstuk 4** hebben we een diepte-analyse verricht van de patiënten met stadium I NSCLC uit de studiepopulatie van hoofdstuk 3. In dit cohort stadium I patiënten vonden we een overeenkomst tussen cTNM en pTNM van 59,9%. Dit betekent dat 40,1% onjuist gestadieerd was. In 22,6% van de patiënten bleek er sprake te zijn van stadium II ziekte of hoger in het pathologische preparaat. Dit is een indicatie voor adjuvante chemotherapie. De overige patiënten die incorrect gestadieerd waren schoven van stadium IA naar stadium IB of vice versa. Bij de patiënten met stadium II ziekte of hoger was er in 14,9% sprake van lymfkliermetastasen (pN1-2), waarbij er in 5,5% sprake was van unforeseen N2 ziekte. Bij patiënten met klinische T2a tumoren was er in 21,3% van de patiënten sprake van lymfkliermetastasen: 14,5% had N1 ziekte, 6,7% had N2 ziekte.

In **Hoofdstuk 5** beschrijven we het stadiëringsproces voor alle patiënten die geopereerd zijn van 2013 tot en met 2015 met pathologische stadium IIIA NSCLC. In deze studie zijn 527 patiënten met stadium IIIA ziekte geïncludeerd, van wie er 254 patiënten unforeseen N2 ziekte hadden (7,1%). In deze 254 patiënten zijn er preoperatief 18 endoscopische echografieën, 62 endobronchiale echografieën en 67 (video)mediastinoscopiën verricht. Slechts een kleine patiëntengroep (n=8) kreeg geen preoperatieve invasieve mediastinale stadiering ondanks verdachte N2 klieren op de PET. Ondanks dat er in richtlijnen geadviseerd wordt om neoadjuvante therapie te geven bij resectabel NSCLC met beperkte N2 ziekte, is dit bij 40 patiënten achterwege gelaten in dit cohort. Helaas bevat de DLCA geen informatie over de besluitvorming hieromtrent.

**Hoofdstuk 6** toont een analyse van 1.729 patiënten, geopereerd tussen 2012 en 2016, die een (video)mediastinoscopie ondergingen tijdens het stadiëringsproces. Hierbij was de primaire onderzoeksvraag of de (video)mediastinoscopie conform de richtlijnen werd uitgevoerd, en of het voorkomen van unforeseen N2 ziekte hieraan gerelateerd was. De Nederlandse richtlijn schrijft voor dat je mediastinale lymfklierbiopten moet nemen van twee ipsilaterale stations, 1 contralateraal station en station 7. De Europese richtlijn schrijft voor dat je station 4 aan de linker en rechter zijde en station 7 moet biopteren. In 51% van de patiënten was de Nederlandse richtlijn gevolgd, in 75% de Europese richtlijn. Bij patiënten die een (video) mediastinoscopie volgens de Nederlandse richtlijnen hadden ondergaan

kwam significant minder unforeseen N2 ziekte voor dan bij patiënten die voldeden aan de Europese richtlijn (8,6% versus 11,9%, p=0.043).

In **Hoofdstuk 7** hebben we data van patiënten van 2013 tot en met 2016 uit de Nederlandse en de Deense nationale databases vergeleken met betrekking tot morbiditeit, mortaliteit en klinisch stadiëren. In Denemarken is de longchirurgie sterk gecentraliseerd (4 ziekenhuizen in 2016), in Nederland is dit niet het geval (43 ziekenhuizen in 2016). Daarnaast hebben beide landen andere bestuurlijk systemen in ziekenhuizen en een andere financiële dekking van de gezondheidszorg. Als we patiënten vergelijken met NSCLC zonder metastasen, die één operatie hebben ondergaan zonder neo-adjuvante therapie, is de 30-dagen mortaliteit vergelijkbaar tussen beide landen (1,5% in Denemarken, 1,9% in Nederland (niet significant), risico gewogen mortaliteit respectievelijk 1,7% en 1,8% (niet significant)). Het percentage patiënten met een gecompliceerd postoperatief beloop was 24,4% en 34,8% in Denemarken en Nederland ($p<0.05$). Echter, het is lastig hier harde uitspraken over te doen bij gebrek aan heldere en overeenkomende data definities. Overeenkomst tussen cTNM en pTNM was in Denemarken 53,0%, tegenover 52,9% in Nederland. Nationale databases zouden idealiter vergelijkbaar moeten zijn, zodat het mogelijk is verschillende gezondheidszorgsystemen en bestuurlijke systemen te kunnen vergelijken, alsmede de effecten van centralisatie. Gezien de verschillende data definities in beide databases is het lastig om op dit moment harde uitspraken te doen over de verschillen tussen Denemarken en Nederland.

**Hoofdstuk 8** bevat een review van de literatuur en onze visie op het stadiëringstraject, en de mogelijke gevolgen voor adjuvante chemotherapie. In stadium I NSCLC is klinisch stadiëren het meest accuraat. Als stereotactische radiotherapie (SABR) overwogen wordt als behandeling bij deze patiënten, zijn er een aantal zaken belangrijk. Mocht een patient bijvoorbeeld onverwachts hilaire (N1) klieren hebben, dan is chirurgische resectie, gevolgd door adjuvante chemotherapie de aangewezen behandeling. Deze therapie geeft een verbeterde 5-jaars overleving van 4%. Wanneer we weten dat in 22,6% van de stadium I patiënten er toch onverwachts stadium II ziekte of hoger is (hoofdstuk 4), wordt dus bijna een kwart van de patiënten adjuvante chemotherapie ontzegd als er gekozen wordt voor SABR als behandeling. Klinische stadium II ziekte maakt mediastinale lymfklierstadiering noodzakelijk, zij het door tumorgrootte,

N1 lymfklieren of centrale lokalisatie van de tumor. Stadiëren van het mediastinum gebeurt als eerste met EBUS. Chirurgie blijft de belangrijkste behandelmodaliteit, waarbij adjuvante chemotherapie met platinum 4% extra 5-jaars overleving geeft. Stadium III ziekte bestaat uit een heterogene groep van tumoren, variërend van kleine tumoren met uitgebreide lymfkliermetastasering in het mediastinum, tot grote tumoren of tumoren met ingroei in vitale structuren zoals wervels en grote bloedvaten. Bij deze patiënten is de kans op occulte afstandsmetastasen groter, dus een MRI van het brein wordt geadviseerd. Afhankelijk van de resectabiliteit van de ziekte kan curatieve behandeling bestaan uit inductietherapie met chirurgische resectie, of definitieve chemoradiotherapie gevolgd door Durvalumab.

In **Hoofdstuk 9** reflecteren we op twee ingezonden meningen van experts naar aanleiding van het artikel dat wordt beschreven in hoofdstuk 8. Onderwerp van de discussie is de indicatie voor adjuvante chemotherapie voor tumoren van een bepaalde grootte. Gezien de resultaten van de CALGB 9633 trial is dit geïndiceerd voor patiënten met een tumor groter dan 4 cm. In de huidige editie van de TNM classificatie is dit duidelijker uitgedrukt door stadium IIA ziekte te laten starten bij tumoren groter dan 4 cm (in TNM 7 startte stadium IIA bij tumoren groter dan 5 cm). Hiernaast wordt er gediscussieerd over herstadiëren na neo-adjuvante therapie. Het advies is om bij patiënten met lokaal gevorderd NSCLC het mediastinum te herstadiëren na inductietherapie voor een operatie, omdat de winst van aanvullende chirurgie bij yN0-1 duidelijker is dan bij patiënten met yN2.

**Hoofdstuk 10** bevat de discussie en toekomstvisie op klinisch stadiëren van niet-kleincellig longkanker: een onderwerp met vele interessante uitdagingen in de nabije toekomst.

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## CURRICULUM VITAE

David Jonathan Heineman was born in Nijmegen, September 14, 1981. He grew up in Klimmen in the south of the Netherlands, where he attended primary school at "Ummer Clumme". Secondary school was started at the "Bernardinuscollege" in Heerlen, but after moving to Glimmen in the 3rd grade, it was finished at the "Willem Lodewijk Gymnasium" in Groningen in the north of the Netherlands. The journey continued to Amsterdam, where he started studying Medicine in 1999 at the University of Amsterdam. After a short period as an orthopaedic resident not in training at the Slotervaartziekenhuis under prof. dr. R.G. Pöll he got accepted into the training in orthopaedic surgery. The first part of his residency included two years of general surgery in Medisch Centrum Alkmaar under dr. W.H. Schreurs. This specialty interested David so much that he decided to switch and got accepted into surgical training at the VU medical center under prof. dr. D.L. van der Peet. The largest part of his residency and the differentiation towards lung surgery took place in Medisch Centrum Alkmaar and he finally certified as a gastro-intestinal, oncological and lung surgeon. After finishing his residencies, surgical training was continued as a fellow in oncological surgery in Rijnstate hospital in Arnhem. In March 2017 he started as a lung surgeon and upper GI surgeon in the VU medical center. Currently, he is still employed in the now called Amsterdam UMC (former VU medical center merged with the Academic Medical Center), participating in the Department of Surgery (prof. dr. H.J. Bonjer) and the Department of Cardiothoracic Surgery (prof. dr. R.J.M. Klautz).

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II